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(54) Pyrazolopyrimidinone antianginal agents

Pyrazolopyrimidone als Wirkstoffe gegen Angina

Pyrazolopyrimidones comme agents antiangineux

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EP 0 526 004 B1

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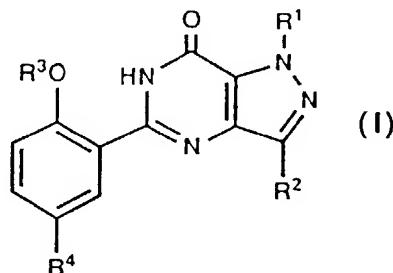
Description

The invention relates to a series of pyrazolo[4,3-d]pyrimidin-7-ones, which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE), having utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

European patent application EP-A-0201188 discloses certain pyrazolo[4,3-d]pyrimidin-7-ones as adenosine receptor antagonists and PDE inhibitors, useful in the treatment of cardiovascular disorders such as heart failure or cardiac insufficiency. However these compounds are neither particularly potent PDE inhibitors, nor are they reported to be selective inhibitors of cGMP PDE.

The compounds of the present invention have the formula (I):



wherein

35 R^1 is H; C_1 - C_3 alkyl optionally substituted with one or more fluoro substituents; or C_3 - C_5 cycloalkyl;

R^2 is H, or C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl;

40 R^3 is C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl; C_3 - C_5 cycloalkyl; C_3 - C_6 alkenyl; or C_3 - C_6 alkynyl;

45 R^4 is C_1 - C_4 alkyl optionally substituted with OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 alkanoyl optionally substituted with NR^5R^6 ; hydroxy C_2 - C_4 alkyl optionally substituted with NR^5R^6 ; $(C_2$ - C_3 alkoxy) C_1 - C_2 alkyl optionally substituted with OH or NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halo; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or phenyl or heterocyclyl either of which is optionally substituted with methyl;

50 R^5 and R^6 are each independently H or C_1 - C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-(NR^9)piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy;

R^7 is H or C_1 - C_4 alkyl;

55 R^8 is C_1 - C_3 alkyl optionally substituted with NR^5R^6 ;

and

R^9 is H; C_1 - C_3 alkyl optionally substituted with phenyl; hydroxy C_2 - C_3 alkyl; or C_1 - C_4 alkanoyl;

and pharmaceutically acceptable salts thereof.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched chain. In addition alkenyl or alkynyl groups having four or more carbon atoms, or alkoxy groups having three carbon atoms, may be straight or branched chain. Halo means fluoro, chloro, bromo or iodo, whilst heterocyclyl is selected from thienyl, pyridyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl or pyrimidinyl.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers

or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

5 Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

10 The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

15 A preferred group of compounds of formula (I) is that wherein R¹ is H, methyl or ethyl; R² is C₁-C₃ alkyl; R³ is C₂-C₃ alkyl; R⁴ is C₁-C₂ alkyl optionally substituted with OH, NR⁵R⁶, CONR⁵R⁶ or CO₂R⁷; acetyl optionally substituted with NR⁵R⁶; hydroxyethyl substituted with NR⁵R⁶; ethoxymethyl optionally substituted with OH or NR⁵R⁶; CH=CHCN; CH=CHCONR⁵R⁶; CH=CHCO₂R⁷; CO₂H; CONR⁵R⁶; Br; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R⁵ and R⁶ are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-(NR⁹)-1-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy; R⁷ is H or t-butyl; R⁸ is methyl or CH₂CH₂CH₂NR⁵R⁶; and R⁹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

20 A particularly preferred group of compounds of formula (I) is that wherein R¹ is methyl; R² is n-propyl; R³ is ethyl or n-propyl; R⁴ is CH₂NR⁵R⁶, CH₂OCH₂CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CO₂H, CONR⁵R⁶, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂NR⁵R⁶, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R⁵ and R⁶ together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-(NR⁹)-1-piperazinyl or 2-methyl-1-imidazolyl group; R⁷ is H or t-butyl; and R⁹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

25 Especially preferred individual compounds of the invention include:

30 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

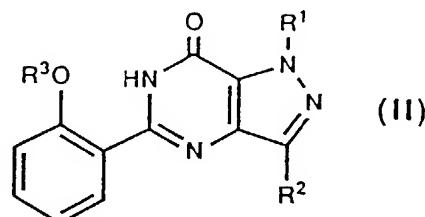
35 5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

40 5-[5-(4-acetyl-1-piperazinyl)acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

45 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

50 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

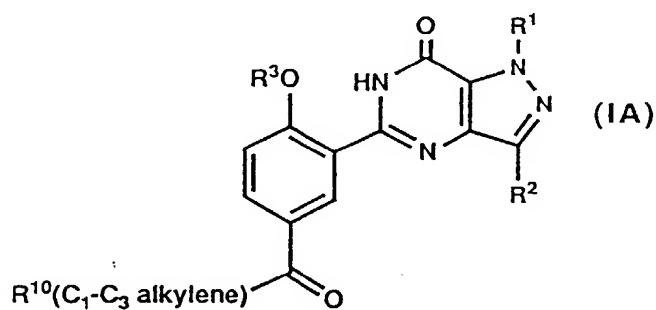
Depending on the nature of R⁴, the compounds of formula (I) may be prepared by a variety of methods from a compound of formula (II):



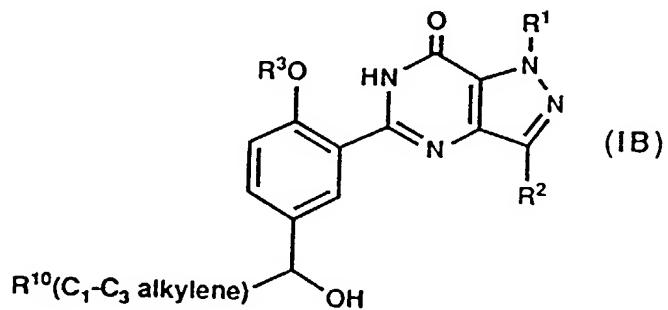
55 wherein R¹, R² and R³ are as previously defined. For example, when R⁴ is C₂-C₄ alkanoyl, the required product is obtainable by conventional Friedel-Crafts acylation whereby (II) is reacted with about a 2-fold excess of an acyl halide of formula (C₁-C₃ alkyl)COY, wherein Y is halo, preferably chloro or bromo, in the presence of about a 3-fold excess of a Lewis acid such as aluminium chloride or aluminium bromide, in a suitable solvent, e.g. dichloromethane, at from about 0°C to the reflux temperature of the reaction medium. When R⁴ is C₂-C₄ alkanoyl substituted with NR⁵R⁶, wherein R⁵ and R⁶ are as previously defined, the product is obtained from (II) via the intermediacy of the corresponding halo-

tone, i.e. a compound of formula (I) wherein R^4 is $CO(C_1\text{-}C_3\text{ alkylene})X$ and X is halo, preferably chloro or bromo, by reaction of the appropriate halo ketone with the required amine of formula R^5R^6NH in the presence of at least one equivalent of base to scavenge the liberated acid by-product (HX), in a suitable solvent, e.g. acetonitrile, at about room temperature. The base may be an inorganic salt such as anhydrous potassium carbonate, a tertiary amine such as triethylamine, or excess reactant amine. In cases wherein either R^5 or R^6 is H, it may be advantageous to use a protected amine of formula R^5NHP or R^6NHP wherein P is a compatible protecting group, e.g. benzyl which can be subsequently removed by catalytic hydrogenation. When both R^5 and R^6 are H, an ammonia equivalent of formula P'_2NH , wherein P' is a protecting group such as t-butoxycarbonyl, may be beneficially employed. In this case, the potassium salt of the non-basic aminating reagent is used for reaction with the halo ketone; deprotection is effected by acidolysis using, for example, hydrogen chloride, which allows convenient isolation of the desired aminoketone as its hydrochloric salt. The intermediate halo ketone is also obtained via Friedel-Crafts chemistry, as described above, in this case between (II) and the appropriate haloacyl halide of formula $X(C_1\text{-}C_3\text{ alkylene})COY$, wherein X and Y are as previously defined.

The above ketones of general formula (IA):

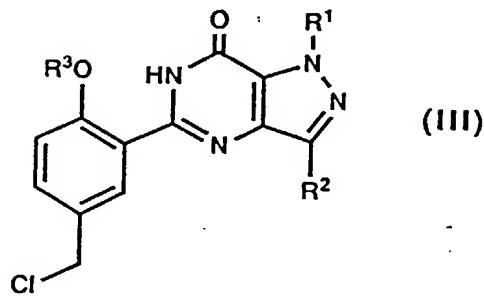


30 wherein R^{10} is either H or NR^5R^6 , and R^1 , R^2 , R^3 , R^5 and R^6 are as previously defined, may be reduced to provide the corresponding alcohol derivatives of general formula (IB):



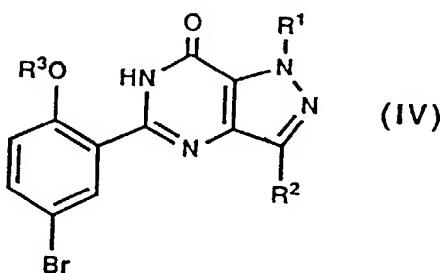
45 wherein R^1 , R^2 , R^3 and R^{10} are as previously defined. The reducing agent is preferably sodium borohydride and the reaction may be conducted in a suitable solvent, e.g. ethanol, at about room temperature.

50 A compound of formula (I) wherein R^4 is hydroxymethyl and R^1 , R^2 and R^3 are as previously defined may be prepared by subjecting a compound of formula (II) to standard chloromethylation conditions, e.g. paraformaldehyde and concentrated hydrochloric acid, at from about room temperature to about 120°C, to provide the intermediate chloromethyl derivative of formula (III), which is then treated with an alkali metal hydroxide, e.g. sodium hydroxide or potassium hydroxide, in a suitable solvent such as an ethylene glycol-dimethyl sulphoxide mixture at from about room temperature to about 100°C.



The above chloromethyl derivatives (III), wherein R¹, R² and R³ are as previously defined, are valuable intermediates in the synthesis of further compounds of formula (I). For example, treatment of (III) with C₂- or C₃- alkanol in the presence of about one equivalent of an alkali metal, preferably sodium, at about room temperature, affords the corresponding C₂- or C₃-alkoxymethyl derivatives respectively. Similarly, when a C₂- or C₃-diol is employed, the analogous hydroxy (C₂- or C₃-alkoxy)methyl compounds are obtained. The latter may be further transformed by activation of the terminal hydroxy group, e.g. by conventional mesylation using about a 10% excess of mesyl chloride, in pyridine as solvent, at from about 0°C to about room temperature, followed by reaction of the mesylate with, for example, an amine of formula R⁵R⁶NH. Preferably the reaction is conducted with up to a 5-fold excess of amine in a suitable solvent, e.g. acetonitrile, at the reflux temperature of the reaction medium. As discussed above, when either R⁵ or R⁶ is H or both are H, an amine protection-deprotection strategy may be profitably employed. Thus are provided compounds of formula (I) wherein R⁴ is (C₂-C₃)alkoxymethyl optionally substituted with either OH or NR⁵R⁶, and R¹, R², R³, R⁵ and R⁶ are as previously defined.

25 The higher homologues of the above compounds, i.e. those compounds of formula (I) wherein R⁴ is (C₂-C₃)alkoxymethyl optionally substituted with either OH or NR⁵R⁶, may be synthesised by similar procedures from the 2-chloroethyl, 2-bromoethyl or 2-mesyloxyethyl analogues of (III) which, in turn, are derivable from the corresponding 2-hydroxyethyl precursor by standard procedures. This precursor may be prepared for example from a compound of formula (I), wherein R⁴ is bromo and R¹, R² and R³ are as previously defined (formula (IV)), by lithium-bromine exchange using n-butyllithium, followed by reaction of the aryllithium intermediate (vide infra) with ethylene oxide.



The chloromethyl intermediates of formula (III) may also be used for the preparation of compounds of formula (I), wherein R⁴ is CH₂NR⁵R⁶ and R¹, R², R³, R⁵ and R⁶ are as previously defined, by reaction with the appropriate amine of formula R⁵R⁶NH (or protected version thereof - vide supra). Preferably the reaction is carried out with about a 3-fold excess of amine in a suitable solvent, e.g. 2-butanone, at from about 0°C to the reflux temperature of the reaction medium. By analogy, compounds of formula (I) wherein R⁴ is (C₂-C₄ alkylene)NR⁵R⁶ may be conveniently obtained from the appropriate chloro, bromo, or mesyloxy precursor which, in turn, is derivable from the corresponding alcohol (see above for a synthetic approach to the 2-hydroxyethyl analogue). The 3-hydroxypropyl and 4-hydroxybutyl analogues may be prepared by catalytic hydrogenation of the alkenols obtained when the above-mentioned bromo compound of formula (IV) is subjected to Heck reaction conditions (vide infra) with allyl alcohol or 3-buten-1-ol respectively.

50 The chloromethyl intermediates may further be employed to furnish the corresponding methyl derivatives, i.e. compounds of formula (I) wherein R⁴ is CH₃ and R¹, R² and R³ are as previously defined. This can be achieved by catalytic hydrogenation using a palladium on charcoal catalyst, in a suitable solvent such as ethyl acetate, at about 50 p.s.i. (3.45 bar) and room temperature. By analogy, when R⁴ is ethyl, n-propyl or n-butyl, such compounds of formula (I) may also be obtained from the corresponding alkyl chlorides derived, in turn, from the appropriate alcohols mentioned above by standard methodology. Other alcohol derivatives, e.g. the corresponding bromide or mesylate, may also be used.

The above bromo derivatives (IV), which are valuable intermediates in the synthesis of yet further compounds of formula (I), may be prepared from a compound of formula (II) by direct bromination in a suitable solvent. This may be achieved, for example, either with about a 60% excess of N-bromosuccinimide in dimethylformamide at room temperature or with a similar excess of bromine in glacial acetic acid at from about room temperature to about 100°C. Alternatively, (IV) and the corresponding fluoro, chloro and iodo analogues may be obtained from the primary amine (*vide infra*) *via* classical sequential diazotisation-halogenation procedures including, for example, the Schiemann, Sandmeyer and Gatterman reactions.

By exploitation of Heck methodology, the bromo intermediate (IV) can be transformed to compounds of formula (I), wherein R⁴ is CH=CHCN, CH=CHCONR⁵R⁶ or CH=CHCO₂R⁷ and R¹, R², R³, R⁵, R⁶ and R⁷ are as previously defined, by employment of acrylonitrile or the appropriate acrylic acid amide or ester derivative. The reaction is generally carried out with about a 50% excess of both the alkene reagent and a tertiary amine such as triethylamine, in the presence of about 0.1 equivalents of a tertiary arylphosphine, preferably tri-*o*-tolylphosphine, and about 0.05 equivalents of palladium(II) acetate, in a suitable solvent such as acetonitrile, at the reflux temperature of the reaction medium. The resulting acrylic esters may be hydrolysed if desired, e.g. using aqueous sodium hydroxide solution, with methanol as co-solvent, to afford the corresponding cinnamic acids. Moreover, all the alkenyl products thus synthesised may be subjected to catalytic hydrogenation, e.g. using 5% palladium on charcoal in a suitable solvent at about 15 p.s.i. (1.0 bar) and room temperature, to provide compounds of formula (I) wherein R⁴ is CH₂CH₂CN, CH₂CH₂CONR⁵R⁶ or CH₂CH₂CO₂R⁷ and R¹, R², R³, R⁵, R⁶ and R⁷ are as previously defined for formula (I). An alternative reduction strategy, in which the acrylonitrile derivative (cinnamonic nitrile analogue) is exhaustively hydrogenated with Raney nickel in glacial acetic acid, affords a compound of formula (I) wherein R⁴ is 3-aminopropyl and R¹, R² and R³ are as previously defined.

The higher homologues, i.e. compounds of formula (I) wherein R⁴ is either C₃-C₄ alkyl or C₃-C₄ alkenyl substituted with CN, CONR⁵R⁶ or CO₂R⁷, or is 4-aminobutyl, may be derived from the previously mentioned alkenols obtained from Heck reactions between the bromo compound of formula (IV) and either allyl alcohol or 3-buten-1-ol. The conventional procedures necessary for transformation of the terminal hydroxyl group *via* a suitably reactive derivative, e.g. the corresponding chloride, bromide or mesylate, to the required functional groups will be well known to persons skilled in the art, and will be equally applicable to the 2-hydroxyethyl analogue (*vide supra*) thereby offering an alternative to Heck methodology. Compounds of formula (I), wherein R⁴ is CH₂CN, CH₂CONR⁵R⁶, CH₂CO₂R⁷ or CH₂CH₂NH₂, may be obtained from the chloromethyl intermediates of formula (III) by reaction with an alkali metal cyanide, e.g. sodium cyanide or potassium cyanide, followed by standard transformations or the resulting nitrile.

As a general alternative to the above Heck reaction approach, the desired alkenes (and derived alkanes *via* catalytic hydrogenation) may be obtained using a Wittig-Horner strategy in which an aldehyde of formula (I), wherein R⁴ is CHO and R¹, R² and R³ are as previously defined, is reacted with the appropriate phosphonium salt or phosphonate in the presence of a suitable base. The aldehyde itself is obtainable for formylation, e.g. using dimethylformamide, of the previously described aryllithium derivative of (IV) and, by analogy, is also a convenient precursor to compounds of formula (I) wherein R⁴ is C₂-C₄ alkenyl or C₂-C₄ alkyl and R¹, R² and R³ are as previously defined.

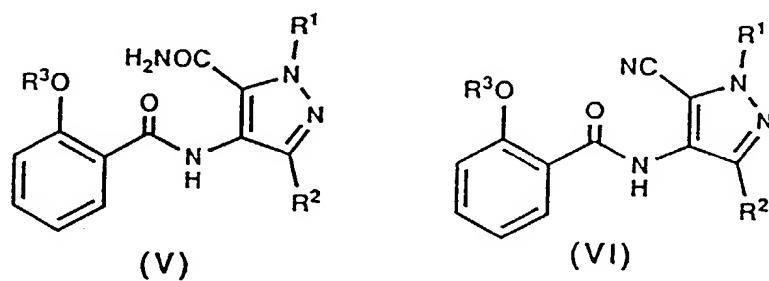
This aryllithium intermediate is also useful in the preparation of compounds of formula (I) wherein R⁴ is CONR⁵R⁶ or CO₂R⁷ and R¹, R², R³, R⁵, R⁶ and R⁷ are as previously defined. For example, lithiation of (IV) in dry tetrahydrofuran at about -78°C using about a 5-fold excess of a solution of n-butyllithium in hexane, quenching of the resulting aryllithium with carbon dioxide at about -40°C, and aqueous work-up at about 0°C including careful acidification to pH 3, furnishes the corresponding benzoic acid derivative. The acid may be activated under mild conditions, such as those obtaining in peptide bond formation *via* amino acid coupling procedures, and converted to an ester or amide derivative as required. For example, activation of the benzoic acid using a carbodiimide/1-hydroxybenzotriazole combination in the presence of the required amine of formula R⁵R⁶NH or alcohol of formula R⁷OH, in a suitable solvent such as dichloromethane at about 0°C to room temperature, yields the corresponding amide or ester respectively.

The bromo intermediates of formula (IV) are also of utility in the synthesis of compounds of formula (I) wherein R⁴ is phenyl or heterocyclyl, each of which is optionally substituted with methyl, and R¹, R² and R³ are as previously defined. When R⁴ is phenyl or C-linked heterocyclyl, it may be introduced *via* palladium-catalysed coupling of the zincate derivative generated *in situ* from the corresponding phenyllithium or heterocyclyllithium intermediate; the latter, in turn, may be obtained from either the heterocycle or haloheterocycle as necessary by treatment with n-butyllithium. Thus, for example, the phenyllithium or heterocyclyllithium (in the presence of about 1 extra equivalent of n-butyllithium to accommodate the active hydrogen atom of the pyrazolopyrimidinone substrate) is treated with about 2 equivalents of anhydrous zinc chloride in dry tetrahydrofuran at about -78°C followed, at about room temperature, by (IV) and the palladium catalyst, preferably tetrakis(triphenylphosphine)palladium(0). The reaction mixture can be heated to reflux with addition of up to about 2 further equivalents of anhydrous zinc chloride if necessary. When R⁴ is N-linked heterocyclyl, the reaction may be conducted with up to about a 5-fold excess of the appropriate heterocycle in the presence of about a 10% excess of base, e.g. anhydrous potassium carbonate, to scavenge the hydrogen bromide by-product, together with about a 10% excess of copper-bronze and about 0.25 equivalents of iodine catalyst in a suitable solvent, e.g. dimethylformamide, at about the reflux temperature of the reaction medium.

Compounds of formula (I), wherein R^4 is $NHSO_2NR^5R^6$ or $NHSO_2R^8$ and R^1 , R^2 , R^3 , R^5 , R^6 and R^8 are as previously defined, may be synthesised from the corresponding primary amine which, in turn, is obtained by nitration of (II) using, e.g. a conventional concentrated nitric acid/concentrated sulphuric acid combination, followed by reduction of the nitroarene by catalytic hydrogenation using conventional procedures. The reaction is generally carried out using equimolar quantities of the primary amine of formula (I), wherein R^4 is NH_2 and R^1 , R^2 and R^3 are as previously defined, and either the required sulphonamoyl halide or alkylsulphonyl halide (preferably the chlorides) of formula $R^5R^6NSO_2halo$ or R^8SO_2halo respectively, in the presence of excess tertiary amine such as triethylamine or pyridine to scavenge the acid by-product, in a suitable solvent, e.g. dichloromethane, at from about 0°C to about room temperature. Pyridine may conveniently function as both base and solvent when desired, and the reaction may be optionally catalysed by the addition of about 0.1 to 0.2 equivalents of a 4-t-aminopyridine such as 4-dimethylaminopyridine. When both R^5 and R^6 are H, the desired product may also be obtained by reaction of the primary amine with sulphonamide in a suitable solvent, e.g. 1,4-dioxan, at about 100°C.

When, in transformations of compounds of formula (II) to compounds of formula (I), R³ is a group susceptible to reaction or removal under the particular conditions employed to introduce R⁴, said R³ group may itself be introduced at the final stage of the synthesis. Thus a phenol of formula (II), wherein R³ is H, and R¹ and R² are as previously defined, which is obtainable for example by Pd⁰-mediated deprotection of the O-allyl analogue, i.e. a compound of formula (II) wherein R³ is allyl, and R¹ and R² are as previously defined, serves as the substrate for the subsequent reactions involved in introducing the various R⁴ substituents. A final O-alkylation of the phenolic group is then necessary to furnish a compound of formula (I), wherein R¹, R², R³ and R⁴ are as previously defined. This may be achieved under standard conditions using the appropriate alkyl chloride, bromide or sulphonate in the presence of a base such as anhydrous potassium carbonate, in a suitable solvent, e.g. 2-butanone, at the reflux temperature of the reaction mixture. Alternatively, the alkylation may be effected under typical Mitsunobu reaction conditions.

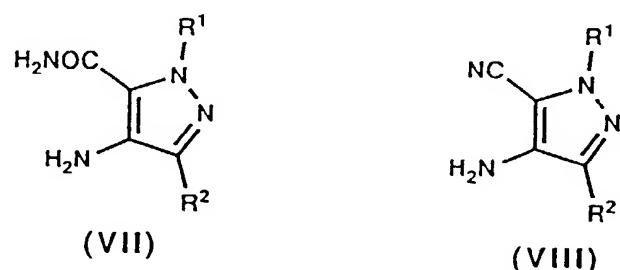
A compound of formula (II) may be prepared from a compound of formula (V):



wherein R¹, R² and R³ are as previously defined, by the application of known cyclisation methods for pyrimidinone ring formation. Thus, for example, the cyclisation may be effected by the treatment of (V) with a base such as sodium hydroxide or potassium carbonate, optionally in the presence of hydrogen peroxide, in an ethanol-water medium at reflux temperature. Under these conditions the related nitrile of formula (VI), wherein R¹, R² and R³ are as previously defined, may also be employed as the precursor to (IV).

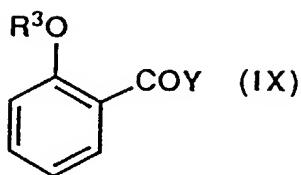
In an alternative cyclisation procedure, compounds of the formula (II) may be obtained by treatment of (V) with polyphosphoric acid at about 140°C.

Compounds of formulae (V) and (VI) may be prepared from compounds of formulae (VII) and (VIII) respectively:



wherein R¹ and R² are as previously defined, by reaction with a compound of formula (IX):

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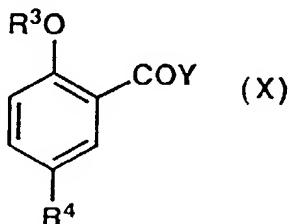
wherein R³ and Y are as previously defined.

The reaction is generally carried out using an excess of (IX) in the presence of an excess of a tertiary amine such as triethylamine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in an inert solvent such as dichloromethane at from about 0°C to room temperature.

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Compounds of formula (I) may be obtained more directly from a compound of formula (X):

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wherein R³, R⁴ and Y are as previously defined, when such acyl halides are readily accessible, by reaction with either (VII) or (VIII) and subsequent ring-closure of the product as described above. Clearly this alternative synthetic route will only be appropriate when R⁴ is compatible with the reaction conditions obtaining in both steps, e.g. when R⁴ is acetyl as illustrated by Example 17.

The aminopyrazoles of formulae (VII) and (VIII), the acyl halides of formulae (IX) and (X), and the intermediates employed for introduction of the various R⁴ substituents into compounds of formula (II) to afford compounds of formula (I), when neither commercially available nor subsequently described, can be obtained by conventional synthetic procedures, in accordance with literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

Certain of the compounds of formula (I), wherein R⁹ is as previously defined but not hydrogen, may be prepared directly from the corresponding 4-N-unsubstituted piperazine analogue, that is the precursor wherein R⁹ is hydrogen, using appropriate standard synthetic procedures.

All of the above reactions are entirely conventional and the necessary reagents and conditions for their performance can readily be established by reference to standard text books and to the Examples provided hereafter. Alternatives and variations will also be evident to persons skilled in the art to enable all the compounds defined by formula (I) to be prepared.

The biological activities of the compounds of the present invention were determined by the following test methods.

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Phosphodiesterase activity

Compound affinities for cGMP and cAMP PDEs are assessed by determination of their IC₅₀ values (the concentration of inhibitor required for 50% inhibition of enzyme activity). The PDE enzymes are isolated from rabbit platelets and rat kidney, essentially by the method of W.J. Thompson *et al.* (Biochem., 1971, 10, 311). The calcium/calmodulin (Ca/CAM)-independent cGMP PDE and the cGMP-inhibited cAMP PDE enzymes are obtained from rabbit platelets whilst, of the four major PDE enzymes of the rat kidney, the Ca/CAM-dependent cGMP PDE (fraction I) is isolated. Assays are performed using a modification of the "batch" method of W.J. Thompson and M.M. Appleman (Biochem., 1979, 18, 5228). Results from these tests show that the compounds of the present invention are potent and selective inhibitors of both cGMP PDEs.

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Platelet anti-aggregatory activity

This is assessed by the determination of a compound's ability to inhibit platelet aggregation *in vitro* induced by

platelet activating factor (PAF), and to potentiate the platelet antiaggregatory action *in vitro* of activators of guanylate cyclase such as nitroprusside and EDRF. Washed platelets are prepared essentially by the method of J.F. Mustard *et al.* (Methods in Enzymol., 1989, 169, 3) and aggregation is determined using standard turbidimetric techniques as described by G.V.R. Born, (J. Physiol. (Lond), 1962, 162, 67P).

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Antihypertensive activity

This is assessed following intravenous or oral administration of a compound to spontaneously hypertensive rats. Blood pressure is recorded *via* a cannula implanted in the carotid artery of either conscious or anaesthetised animals.

10 For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 15 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

20 For human use, the compounds of formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixtures with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. The compounds may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

25 Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

30 The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for use in medicine.

35 The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, 40 chronic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS.

45 In a further aspect, the invention provides a method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

50 The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations. The purity of the compounds was routinely monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F₂₅₄ plates. ¹H-Nuclear magnetic resonance spectra were recorded using either a Nicolet QE-300 or a Bruker AC-300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

5-(2-Ethoxy-5-piperidinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

55 Piperidine (0.22 ml, 0.0022 mol) was added to a stirred suspension of 5-(5-bromoacetyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 8, 0.95 g, 0.0022 mol) and anhydrous potassium carbonate (0.6 g, 0.0044 mol) in acetonitrile (50 ml) at room temperature. After 18 hours the mixture was evaporated under vacuum, the residue dissolved in water (50 ml) and the solution extracted with ethyl acetate (3 x 30 ml). The organic extracts were combined, washed with brine (3 x 20 ml), dried (Na₂SO₄) and evaporated under vacuum. The resulting yellow solid was chromatographed on silica gel (12 g), using a methanol in dichloromethane elution gradient (0-2% methanol), to give an off-white solid. Crystallisation from ethyl acetate-hexane gave the title compound

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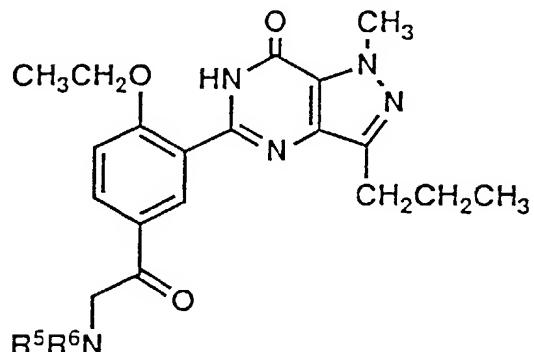
as an off-white powder (0.27 g, 28%), m.p. 149-151°C. Found: C,66.13; H,6.90; N,15.95. $C_{24}H_{31}N_5O_3$ requires C, 65.88; H,7.14; N,16.01%.

EXAMPLES 2-8

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The following Examples were prepared by the procedure of Example 1 using the appropriate amine.

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| Example | NR ⁵ R ⁶ | % yield | m.p. (°C) | Analysis % (theoretical in brackets) | | |
|---------|--|------------|--------------|---|--------------|------------------|
| | | | | C | H | N |
| 2 | N(CH ₂ CH ₃) ₂ | 4 | 120-121 | 65.21 (64.92 | 7.31 7.34 | 16.37 16.46) |
| 3 | | 23 | 183-185 | 62.48 (62.48 | 6.62 6.71 | 17.32 17.49) |
| 4 | | 29 | 159-160 | 63.20 (62.85 | 6.58 6.65 | 15.87 15.94) |
| 5 | | 21 | 202-204 | 61.84 (62.28 | 6.12 6.14 | 18.68 18.95)a |
| 6 | | 39 | 142-143 | 62.83 (63.00 | 7.09 6.90 | 18.90 19.16) |

| Example | NR ⁵ R ⁶ | % yield | m.p. (°C) | Analysis % (theoretical in brackets) | | |
|---------|--------------------------------|------------|--------------|---|--------------|-----------------|
| | | | | C | H | N |
| 7 | | 36 | 135-136 | 62.46 (62.22) | 6.91 7.10 | 17.36 17.41) |
| 8 | | 40 | 151-152 | 63.64 (63.56) | 6.80 6.89 | 15.63 15.44) |

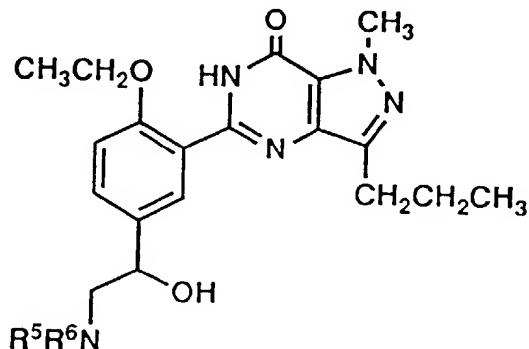
a 0.50 H₂O

EXAMPLE 95-{2-Ethoxy-5-[1-hydro-2-(1-piperazinyl)ethyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5 Sodium borohydride (0.01 g, 0.0027 mol) was added to a stirred suspension of 5-[2-ethoxy-5-(1-piperazinylacetyl)phenyl]-1-methyl-3-n-propyl-1, 6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.12 g, 0.0027 mol) in ethanol (10 ml) and the resulting solution stirred at room temperature for 18 hours. The solvent was removed by evaporation under vacuum, the residue suspended in saturated aqueous sodium carbonate solution (50 ml) and this mixture extracted with dichloromethane (3 x 20 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give an oil. Trituration with ether gave a white solid, crystallisation of which from ethyl acetate-hexane gave the title compound as a white powder (0.050 g, 42%), m.p. 139-140°C. Found: C, 62.55; H, 7.44; N, 18.79. $\text{C}_{23}\text{H}_{32}\text{N}_6\text{O}_3$ requires C, 62.71; H, 7.32; N, 19.08%.

15 EXAMPLES 10-13

The following Examples were prepared by the procedure of Example 9 using the appropriate ketones (Examples 3, 4, 5 and 1 respectively).



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| Example | NR^5R^6 | % yield | m.p. (°C) | Analysis % | | |
|---------|-----------------------------|------------|--------------|------------------|--------------|--------------------------------|
| | | | | C | H | N (theoretical in brackets) |
| 10 | <chem>CN1CCCC1C(=O)N</chem> | 37 | 139-141 | 61.92 (62.22) | 7.01 7.10 | 17.08 17.42) |
| 11 | <chem>CN1CCCC1O</chem> | 69 | 125-127 | 62.23 (62.56) | 7.10 7.08 | 15.53 15.86) |
| 12 | <chem>CN1=CC=CC1</chem> | 77 | 221-222 | 63.68 (63.29) | 6.39 6.47 | 19.17 19.25) |
| 13 | <chem>C1CCCC1</chem> | 97 | 117-118 | 65.51 (65.58) | 7.57 7.57 | 15.84 15.93) |

EXAMPLE 141-Methyl-5-(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5 This compound was prepared from morpholine and 5-(5-bromoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 11), following the procedure of Example 1, and was obtained as white crystals (47%), m.p. 128-129°C. Found: C, 63.62; H, 7.07; N, 15.53. $C_{24}H_{31}N_5O_4$ requires C, 63.56; H, 6.89; N, 15.44%.

EXAMPLE 151-Methyl-5-[5-(4-methyl-1-piperazinylacetyl)-2-n-propoxyphenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

15 This compound was prepared from 4-methylpiperazine and 5-(5-bromoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 11), following the procedure of Example 1, and was obtained as a white solid (27%), m.p. 124-125°C. Found: C, 63.96; H, 7.19; N, 17.80. $C_{25}H_{34}N_6O_3$ requires C, 64.36; H, 7.34; N, 18.01%.

EXAMPLE 165-[5-(1-Hydroxy-2-morpholinoethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

25 This compound was prepared from 1-methyl-5-(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, following the procedure of Example 9, and was obtained as a white solid (28%), m.p. 104-105°C. Found: C, 62.90; H, 7.50; N, 15.48. $C_{24}H_{33}N_5O_4$ requires C, 63.28; H, 7.30; N, 15.37%.

EXAMPLE 175-(5-Acetyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

30 The title compound was prepared from 4-(5-acetyl-2-ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide (Preparation 15), following the procedure of Preparation 7, and was obtained as a white solid (77%), m.p. 196-198°C. Found: C, 64.35; H, 6.16; N, 15.85. $C_{19}H_{22}N_4O_3$ requires C, 64.39; H, 6.26; N, 15.81%.

EXAMPLE 185-(5-Bromo-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

40 N-Bromosuccinimide (2.6 g, 0.016 mol) in dimethylformamide (40 ml) was added dropwise to a stirred solution of 5-(2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 10, 4.0 g, 0.010 mol) in dimethylformamide (40 ml) at room temperature. After 7 hours the solvent was removed by evaporation under vacuum, the residue suspended in saturated aqueous sodium carbonate solution, and the resulting solution extracted with ethyl acetate (3 x 50 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum. Trituration of the residue with ether, followed by crystallisation from ethyl acetate-hexane, gave the title compound as white crystals (3.39 g, 68%), m.p. 117-118°C. Found: C, 53.15; H, 5.03; N, 13.78. $C_{18}H_{21}BrN_4O_2$ requires C, 53.34; H, 5.22; N, 13.82%.

EXAMPLE 19(E)-3-(1-Methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-n-propoxycinnamic acid t-butyl ester

55 To a solution of 5-(5-bromo-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (1.0 g, 0.0025 mol) and triethylamine (0.38 g, 0.0038 mol) in acetonitrile (2 ml), was added palladium(II) acetate (0.03 g, 0.00013 mol), tri-o-tolylphosphine (0.076 g, 0.00025 mol) and t-butyl acrylate (0.48 g, 0.0038 mol). The mixture was heated under reflux for 4 hours, then cooled and evaporated under vacuum. The residue was suspended in water

(30 ml) and extraction with dichloromethane (3 x 20 ml) effected. The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give a yellow-green solid. Chromatography on silica gel (12 g), using a methanol in dichloromethane elution gradient (0-2% methanol), followed by crystallisation from ethyl acetate-hexane gave the title compound as a white solid (0.65 g, 58%), m.p. 167-168°C. Found: C, 66.47; H, 7.00; N, 12.31. $\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_4$ requires C, 66.35; H, 7.13; N, 12.38%.

EXAMPLE 20

(E)-3-(1-Methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-n-propoxycinnamic acid

2N Aqueous sodium hydroxide solution (2.28 ml, 0.0046 mol) was added to a solution of (E)-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-n-propoxycinnamic acid t-butyl ester (0.40 g, 0.00088 mol) in methanol (2.3 ml) and the mixture was heated under reflux for 18 hours. The methanol was removed by evaporation under vacuum, the residue dissolved in water (25 ml), and the solution extracted with ethyl acetate (4 x 15 ml). The aqueous layer was separated, acidified to pH 1 with hydrochloric acid, and then extracted with a mixture of methanol and ethyl acetate (3:97, 4 x 20 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum, then the residue crystallised from ethyl acetate to give the title compound as a white solid (0.27 g, 77%), m.p. 229-230°C. Found: C, 63.64; H, 5.98; N, 14.14. $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_4$ requires C, 63.46; H, 6.34; N, 14.10%.

EXAMPLE 21

5-(5-Bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Bromine (0.93 g, 0.0058 mol) was added dropwise to a stirred solution of 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 7, 1.1 g, 0.00352 mol) in glacial acetic acid (20 ml). The mixture was stirred at 100°C for 6.5 hours and the solvent was then removed by evaporation under vacuum. The residue was dissolved in a 9:1 mixture of methanol in dichloromethane (50 ml), and the solution washed with saturated aqueous sodium bicarbonate solution (50 ml), water (50 ml) and saturated brine (50 ml), then dried (MgSO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (15 g) eluting with a mixture of methanol and dichloromethane (1:99) to give, after crystallisation from acetonitrile, the title compound (0.62 g, 45%), m.p. 157-159°C. Found: C, 52.41; H, 5.25; N, 14.01. $\text{C}_{17}\text{H}_{19}\text{BrN}_4\text{O}_2$ requires C, 52.18; H, 4.89; N, 14.32%.

EXAMPLE 22

(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid t-butyl ester

The title compound was prepared from 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one following the procedure of Example 19 and was obtained as a white crystalline solid (31%), m.p. 179-180°C. Found: C, 65.83; H, 6.90; N, 12.75. $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_4$ requires C, 65.89; H, 6.68; N, 12.81%.

EXAMPLE 23

(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid

The title compound was prepared from (E)-4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid t-butyl ester following the procedure of Example 20 and was obtained as white crystals (66%), m.p. 234-236°C. Found: C, 63.01; H, 5.59; N, 14.62. $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_4$ requires C, 62.82; H, 5.80; N, 14.65%.

EXAMPLE 24

3-[4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl]propanoic acid

A solution of (E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid (0.426 g, 0.0011 mol) in a mixture of methanol (28.5 ml), ethyl acetate (100 ml) and water (1.5 ml), was stirred with 5% palladium on charcoal catalyst (0.05 g) under a hydrogen atmosphere at room temperature and pressure for 3 hours. The catalyst was removed by filtration and the solvent removed by evaporation under vacuum. Crystallisation of the residue from ethyl acetate-hexane gave the title compound as beige crystals (0.23 g, 54%), m.p. 165-167°C. Found: C, 62.24; H, 6.17; N, 14.09. $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_4$ requires C, 62.39; H, 6.33; N, 14.41%

EXAMPLE 25(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-5-yl)cinnamic acid dimethylamide

5 The title compound was prepared from N,N-dimethylacrylamide and 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one following the procedure of Example 19 and was obtained, following crystallisation from ethyl acetate-hexane, as colourless crystals (38%), m.p. 219-221°C. Found: C,64.15; H, 6.46; N,16.96. $C_{22}H_{27}N_5O_3$ requires C,64.53; H,6.65; N, 17.10%.

EXAMPLE 263-[4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl]propanoic acid dimethylamide

15 The title compound was prepared from (E)-4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid dimethylamide following the procedure of Example 24 and, after crystallisation from ethyl acetate-hexane, was obtained as colourless crystals (74%), m.p. 155-157°C. Found: C,64.09; H,7.04; N,16.71. $C_{22}H_{29}N_5O_3$ requires C,64.21; H,7.10; N,17.02%.

EXAMPLE 27(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo-4,3-d]pyrimidin-5-yl)cinnamonic nitrile

20 The title compound was prepared from acrylonitrile and 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one following the procedure of Example 19 and was obtained as off-white crystals (33%). Found: C,65.99; H,5.52; N,19.07. $C_{20}H_{21}N_5O_2$ requires C,66.10; H,5.82; N,19.27%.

EXAMPLE 285-[5-(3-Aminopropyl)-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

25 A solution of (E)-4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin- 5-yl)cinnamonic nitrile (0.25 g, 0.00064 mol) in glacial acetic acid (25 ml) was stirred with Raney nickel catalyst (25 mg) under hydrogen at room temperature and at 50 p.s.i. for 3 hours. The resulting mixture was filtered and the filtrate evaporated under vacuum. The residue was partitioned between saturated aqueous sodium carbonate solution (50 ml) and dichloromethane (30 ml), the layers separated and the aqueous phase further extracted with dichloromethane (2 x 30 ml). The organic solutions were combined, dried (Na_2SO_4) and evaporated under vacuum to give a brown solid, crystallisation of which from hexane-ethyl acetate gave the title compound as fawn crystals (96 mg, 38%), m.p. 115-117°C. Found C,65.29; H,7.35; N,18.66. $C_{20}H_{22}N_5O_2$ requires C,65.02; H,7.37; N,18.96%.

EXAMPLE 294-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)benzoic acid

45 *n*-Butyllithium (2.5 M solution in hexane, 1.53 ml, 0.0038 mol) was added dropwise to a stirred solution of 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.60 g, 0.00074 mol) in dry tetrahydrofuran (25 ml) at -78°C under a dry nitrogen atmosphere. After 0.3 hour at -78°C, the solution was allowed to warm to -40°C and carbon dioxide gas was bubbled through the solution. The resulting solution was allowed to warm to room temperature and then poured into water; acidification to pH 3 with 2N hydrochloric acid and extraction with a 9:1 mixture of dichloromethane and methanol (4 x 50 ml) were then effected. The organic extracts were combined, dried ($MgSO_4$) and evaporated under vacuum to give a colourless solid. Chromatography of this solid on silica gel (20 g), using a methanol in dichloromethane elution gradient (2-5% methanol), gave a solid which was dissolved in a 9:1 mixture of dichloromethane and methanol (50 ml); this solution was then washed with saturated aqueous sodium carbonate solution (50 ml), dried ($MgSO_4$) and evaporated under vacuum to give the title compound as a white powder (0.144 g, 26%), m.p. 285-288°C. Found: C,60.74; H,5.72; N,15.61. $C_{18}H_{20}N_4O_4$ requires C,60.66; H,5.66; N,15.72%.

EXAMPLE 305-[2-Ethoxy-5-(4-methylpiperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5 A solution of 4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)benzoic acid (0.095 g, 0.00027 mol), 1-methylpiperazine (0.265 g, 0.00265 mol), 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (0.077 g, 0.0004 mol) and 1-hydroxybenzotriazole (0.054 g, 0.0004 mol) in dichloromethane (25 ml) was stirred at room temperature for 18 hours. The reaction solution was washed with water (25 ml), dried (MgSO_4) and evaporated under vacuum, and then the resulting residue crystallised from ethyl acetate-hexane to give the title compound as colourless crystals (0.03 g, 25%), m.p. 196-197°C. Found: C,63.12; H,6.81; N,18.96. $\text{C}_{23}\text{H}_{30}\text{N}_6\text{O}_3$ requires C,62.99; H,6.90; N,19.16%.

EXAMPLE 315-[2-Ethoxy-5-(1-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

15 A solution of 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.20 g, 0.00051 mol), imidazole (0.172 g, 0.0025 mol), anhydrous potassium carbonate (0.077 g, 0.00056 mol), copper bronze (0.036 g, 0.00057 mol) and iodine (0.015 g, 0.00012 mol) in dimethylformamide (10 ml) was heated under reflux under nitrogen for 4.5 hours, cooled and poured into water (50 ml). This mixture was extracted with a 9:1 mixture of dichloromethane and methanol (6 x 50 ml) and the extracts combined, dried (MgSO_4) and evaporated under vacuum to give a pale brown oil. The oil was chromatographed on silica gel (20 g), eluting with a mixture of dichloromethane, methanol and triethylamine (97.8:2:0.2), to give a yellow solid, crystallisation of which from ethyl acetate-hexane gave the title compound as a cream solid (0.073 g, 38%), m.p. 193-194°C. Found: C,63.61; H,5.97; N,22.03. $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}_2$ requires C,63.48; H,5.86; N,22.21%.

EXAMPLE 325-[2-Ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

30 n -Butyllithium (1.6 M solution in hexane, 9.6 ml, 0.0153 mol) was added to a stirred solution of 1-methylimidazole (0.628 g, 0.0077 mol) in dry tetrahydrofuran (10 ml) at -78°C, and the resulting solution stirred for 0.25 hours. A solution of anhydrous zinc chloride (2.08 g, 0.0153 mol) in dry tetrahydrofuran (15 ml) was added, the mixture allowed to warm to room temperature, then 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (1.0 g, 0.0026 mol) and tetrakis(triphenylphosphine)palladium(0) (0.036 g, 0.031 mol) were added and the mixture heated under reflux for 18 hours. A further quantity of anhydrous zinc chloride (2.08 g, 0.0153 mol) was added and the resulting mixture heated under reflux for a further 60 hours, then cooled; methanol (2 ml) was added and the solvent removed by evaporation under vacuum. The residue was heated with a solution of disodium ethylenediaminetetraacetic acid dihydrate (23.0 g, 0.0618 mol) in water (100 ml) to 100°C for 0.2 hour, then the resulting solution basified to pH 8 with saturated aqueous sodium carbonate solution and extracted with dichloromethane (6 x 100 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give a yellow solid, purification of which by chromatography on silica gel (13 g), using a methanol-dichloromethane elution gradient (0-3% methanol), followed by crystallisation from ethyl acetate, gave the title compound as an off-white solid (0.542 g, 53%), m.p. 199-202°C. Found: C,64.45; H,6.27; N,21.56. $\text{C}_{21}\text{H}_{24}\text{N}_6\text{O}_2$ requires C,64.27; H,6.16; N,21.42%.

EXAMPLE 335-[2-Ethoxy-5-(2-pyridyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

50 The title compound was prepared from 2-bromopyridine and 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, following the procedure described in Example 32, and was obtained as an off-white solid (33%), m.p. 216-218°C. Found: C,67.61; H,5.81; N,17.63. $\text{C}_{22}\text{H}_{23}\text{N}_5\text{O}_2$ requires C,67.85; H,5.95; N,17.98%.

EXAMPLE 341-Methyl-5-(5-morpholinomethyl-2-n-propoxypyhenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5 A solution of 5-(5-chloromethyl-2-n-propoxymethyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 16, 0.60 g, 0.0016 mol) in 2-butanone (10 ml) was added dropwise to a stirred solution of morpholine (0.42 g, 0.0048 mol) in 2-butanone (40 ml) at 0°C. The solution was then heated under reflux for 16 hours, cooled and evaporated under vacuum. The residue was suspended in water (50 ml) and the suspension extracted with ethyl acetate (3 x 20 ml). The organic extracts were combined, washed with brine (2 x 30 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (12 g), using an elution gradient of methanol in dichloromethane (0-2% methanol), to give an oil which solidified on trituration with hexane. Crystallisation from ethyl acetate-hexane gave the title compound as a colourless solid (0.36 g, 53%), m.p. 106-107°C. Found: C, 64.76; H, 7.34; N, 16.36. $\text{C}_{23}\text{H}_{31}\text{N}_5\text{O}_3$ requires C, 64.92; H, 7.34; N, 16.46%.

EXAMPLE 351-Methyl-5-[5-(4-methyl-1-piperazinylmethyl)-2-n-propoxypyhenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

20 The title compound was prepared from 5-(5-chloromethyl-2-n-propoxypyhenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and 1-methylpiperazine, following the procedure of Example 34, and was obtained as a colourless solid (36%), m.p. 149-150°C. Found: C, 65.68; H, 7.83; N, 19.10. $\text{C}_{24}\text{H}_{34}\text{N}_6\text{O}_2$ requires C, 65.73; H, 7.81; N, 19.16%.

EXAMPLE 361-Methyl-5-(5-methyl-2-n-propoxypyhenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

30 A solution of 5-(5-chloromethyl-2-n-propoxypyhenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.5 g, 0.0013 mol) in ethyl acetate (50 ml) was stirred with 10% palladium on charcoal catalyst under a hydrogen atmosphere at 50 p.s.i. and room temperature. After 1 hour, the mixture was filtered and the filtrate evaporated under vacuum to give a pale green solid. Chromatography on silica gel (4 g) using a methanol in dichloromethane elution gradient gave a white solid, crystallisation of which from hexane-ethyl acetate gave the title compound as colourless needles (0.12 g, 26%), m.p. 115-116°C. Found: C, 66.66; H, 7.12; N, 16.55. $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_2$ requires C, 67.04; H, 7.11; N, 16.46%.

EXAMPLE 375-(5-Hydroxymethyl-2-n-propoxypyhenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

40 To a solution of 5-(5-chloromethyl-2-n-propoxypyhenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.5 g, 0.0013 mol) in dimethyl sulphoxide (10 ml) was added sodium hydroxide (0.26 g, 0.0065 mol) and ethylene glycol (0.41 g, 0.0065 mol). The reaction mixture was heated at 100°C for 6 hours, allowed to cool and poured into water (50 ml), then the aqueous mixture extracted with ethyl acetate (3 x 30 ml). The combined extracts were filtered, dried (Na_2SO_4) and evaporated under vacuum to provide an oil which was purified by chromatography on silica gel (6 g), using a methanol in dichloromethane elution gradient (0-3% methanol). The solid product was crystallised from hexane-ethyl acetate to afford the title compound as a white solid (2%), m.p. 174-175°C. Found: C, 63.97; H, 6.66; N, 15.57. $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_3$ requires C, 64.03; H, 6.79; N, 15.72%.

EXAMPLE 385-(5-Ethoxymethyl-2-n-propoxypyhenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

55 Sodium (0.15 g, 0.0013 mol) was added portionwise to ethanol (40 ml) over 1 hour. 5-(5-Chloromethyl-2-n-propoxypyhenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.5 g, 0.0013 mol) was then added to the solution and, after 3 days at room temperature, the solvent was removed by evaporation under vacuum. The residual solid was suspended in water (50 ml) and the suspension extracted with ethyl acetate (3 x 30 ml). The extracts were then combined, dried (Na_2SO_4) and evaporated under vacuum to give a green solid. Chromatography on silica

gel (6 g) using a methanol in dichloromethane elution gradient gave, after crystallisation of the required product from a hexane-ethyl acetate mixture, the title compound as a white solid (0.2 g, 39%) m.p. 89-90°C. Found: C,65.87; H, 7.57; N,14.66. $C_{21}H_{28}N_4O_3$ requires C,65.60; H,7.34; N,14.57%.

5 EXAMPLE 39

5-[5-(2-Hydroxyethoxymethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

10 This compound was prepared from 5-(5-chloromethyl-2-n-propoxy-phenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and ethylene glycol following the procedure of Example 38 and was obtained as a white solid (45%), m.p. 101-102°C. Found: C,63.13; H,6.88; N,13.98. $C_{21}H_{28}N_4O_4$ requires C,62.98; H,7.05; N,13.99%.

15 EXAMPLE 40

1-Methyl-5-[5-(2-morpholinoethoxymethyl)-2-n-propoxyphenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

20 (a) Methanesulphonyl chloride (0.56 g, 0.0049 mol) was added to a stirred solution of 5-[5-(2-hydroxyethoxymethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (1.8 g, 0.0045 mol) in pyridine (25 ml) at 0°C. After 18 hours at room temperature, the solvent was removed by evaporation under vacuum and the residue partitioned between 2N hydrochloric acid (30 ml) and dichloromethane (30 ml). The aqueous layer was separated and extracted with dichloromethane (2 x 30 ml), then the organic solutions combined, dried (Na_2SO_4) and evaporated under vacuum to give a brown oil. Chromatography on silica gel (12 g) using a methanol in dichloromethane elution gradient (0-3% methanol) gave an oil, trituration of which with hexane, followed by crystallisation from hexane-ethyl acetate, gave the required mesylate as white crystals (0.19 g, 9%), m.p. 74-76°C. Found: C,55.71; H,6.25; N,11.69. $C_{22}H_{30}N_4O_6S$ requires C,55.21; H,6.32; N,11.71%.

30 (b) Morpholine (0.19 g, 0.0021 mol) was added to a solution of the above mesylate, namely 5-[5-(2-methanesulphonyloxyethoxymethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, (0.20 g, 0.00042 mol) in acetonitrile (25 ml) and the stirred mixture was heated under reflux for 18 hours. The solvent was removed by evaporation under vacuum, the residue dissolved in saturated aqueous sodium carbonate solution and the solution extracted with ethyl acetate (3 x 20 ml). The extracts were combined, dried (Na_2SO_4) and evaporated under vacuum, and the residue was chromatographed on silica gel (4 g) using an elution gradient of methanol in dichloromethane (0-2% methanol). Evaporation under vacuum of the appropriate fractions, followed by crystallisation from hexane, gave the title compound as white crystals (0.098 g, 48%), m.p. 65-66°C. Found: C,64.17; H,7.69; N,14.96. $C_{25}H_{35}N_5O_4$ requires C,63.94; H,7.51; N,14.91%.

40 EXAMPLE 41

5-(2-Ethoxy-5-methanesulphonamidophenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

45 Methanesulphonyl chloride (0.157 g, 0.00137 mol) was added to a stirred solution of 5-(5-amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.45 g, 0.00137 mol) in dry pyridine (30 ml) at 0°C. The mixture was stirred for 18 hours at room temperature and then evaporated under vacuum. The residue was suspended in saturated aqueous sodium bicarbonate solution (50 ml) and the mixture extracted with dichloromethane (2 x 30 ml). The organic extracts were combined, washed with brine (2 x 30 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was triturated with ether, chromatographed on silica gel (12 g), eluting with a 98.5:1.5 mixture of dichloromethane and methanol, and the required product crystallised from ethyl acetate-hexane to give the title compound as a white powder (0.32 g, 58%), m.p. 205-206°C. Found: C,53.63; H,5.66; N,17.24. $C_{18}H_{23}N_5O_4S$ requires C, 53.32; H,5.72; N,17.27%.

55 EXAMPLE 42

5-[2-Ethoxy-5-(3-morpholinopropylsulphonamido)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound was prepared from 5-(5-amino-2-ethoxyphenyl)1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo

[4,3-d]pyrimidin-7-one and 3-morpholinopropylsulphonyl chloride, following the procedure of Example 41, and was obtained as brown crystals (14%), m.p. 157-159°C. Found: C,55.42; H,6.53; N,16.01. $C_{24}H_{34}N_6O_5S$ requires C,55.58; H,6.61; N,16.21%.

5 EXAMPLE 43

5-[2-Ethoxy-5-(4-methyl-1-piperazinyl)sulphonamidophenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

10 The title compound was prepared from 4-methyl-1-piperazinylsulphonyl chloride and 5-(5-amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, following the procedure of Example 41, and was obtained as an orange powder (13%), m.p. 152-153°C. Found: C,54.32; H,6.38; N,19.88. $C_{22}H_{31}N_7O_4S$ requires C, 53.97; H,6.38; N,20.03%.

15 EXAMPLE 44

5-[5-(4-Benzyl-1-piperazinylsulphonamidophenyl)-2-ethoxy]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

20 4-Benzyl-1-piperazinylsulphonyl chloride (Preparation 19, 0.9 g, 0.0029 mol) was added to a stirred solution of 5-(5-amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.94 g, 0.0029 mol), 4-dimethylaminopyridine (0.050 g, 0.00041 mol) and triethylamine (1.09 g, 0.0108 mol) in dichloromethane (50 ml). The solution was stirred at room temperature for 48 hours and then evaporated under vacuum. The residue was suspended in saturated aqueous sodium bicarbonate solution (50 ml) and the suspension extracted with dichloromethane (3 x 30 ml). The organic extracts were combined, washed successively with saturated aqueous sodium bicarbonate solution (2 x 20 ml) and brine (3 x 20 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (20 g) using a methanol in dichloromethane elution gradient (0-4% methanol), and the required product crystallised from ethyl acetate-hexane to give the title compound as an off-white powder (0.185 g, 11%). Found: C,58.30; H,6.20; N,16.80. $C_{28}H_{35}N_7O_4S$; 0.5H₂O requires C,58.52; H,6.31; N,17.06%.

30 PREPARATION 1

1-Methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester

35 A mixture of 3-n-propylpyrazole-5-carboxylic acid ethyl ester (24.1 g, 0.132 mol) (prepared by the method of Chem. Pharm. Bull., 1984, 32, 1568) and dimethyl sulphate (16.8 g, 0.133 mol) were heated to 90°C for 2.5 hours. The mixture was dissolved in dichloromethane and the solution washed with aqueous sodium carbonate solution. The organic phase was separated, dried ($MgSO_4$) and evaporated under vacuum to give a solid. Chromatography on silica gel (300 g), eluting with dichloromethane, gave the product as a colourless oil (20.4 g, 79%). Rf 0.8 (silica, dichloromethane, methanol, acetic acid; 80:20:1).

40 PREPARATION 2

1-Methyl-3-n-propylpyrazole-5-carboxylic acid

45 1-Methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester (20.2 g, 0.10 mol) was suspended in 6N aqueous sodium hydroxide solution (50 ml, 0.30 mol). The mixture was heated to 80°C for 2 hours then diluted with water (50 ml) and acidified with concentrated hydrochloric acid (25 ml). Filtration gave the carboxylic acid as pale brown crystals (12.3 g, 71%), m.p. 150-154°C. Found: C,56.99; H,7.25; N,16.90. $C_8H_{12}N_2O_2$ requires C,57.13; H,7.19; N,16.66%.

50 PREPARATION 3

1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxylic acid

55 1-Methyl-3-n-propylpyrazole-5-carboxylic acid (12.1 g, 0.072 mol) was added portionwise to a mixture of oleum (13 ml) and fuming nitric acid (11 ml), keeping the temperature below 60°C. After the addition, the mixture was heated at 60°C overnight and then cooled to room temperature before being poured onto ice; filtration then gave the nitro-pyrazole as a white solid (11.5 g, 75%), m.p. 124-127°C. Found: C,45.43; N,5.22; N,19.42. $C_8H_{11}N_3O_4$ requires C,

45.57; H,5.20; N,19.71%.

PREPARATION 4

5 1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxamide

10 1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxylic acid (11.3 g, 0.053 mol) was added to thionyl chloride (50 ml) and the resulting mixture heated under reflux for 3 hours. The reaction mixture was then cooled and excess thionyl chloride removed by evaporation under vacuum. The oily residue was dissolved in acetone (50 ml) and the solution cautiously added to a mixture of ice (50 g) and concentrated aqueous ammonium hydroxide solution (50 ml). The precipitate was collected by filtration to provide the pyrazolecarboxamide as a pale yellow solid (8.77 g, 78%), m.p. 141-143°C. Found: C,45.22; H,5.71; N,26.12. $C_8H_{12}N_4O_3$ requires C,45.28; H,5.70; N,26.40%.

PREPARATION 5

15 4-Amino-1-methyl-3-n-propylpyrazole-5-carboxamide

20 1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxamide (3.45 g, 16.2 mmol) and stannous chloride dihydrate (18.4 g, 81 mmol) were suspended in ethanol and the mixture heated under reflux for 2 hours. The resulting solution was cooled to room temperature, basified to pH 9 by the addition of 2N aqueous sodium hydroxide solution and extracted with dichloromethane (3 x 150 ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated under vacuum. Trituration of the residue with ether gave the aminopyrazole as an off-white solid (2.77 g, 94%), m.p; 98-101°C. Found: C,52.84; H,7.81; N,30.38. $C_8H_{14}N_4O$ requires C,52.73; H,7.74; N,30.75%.

25 PREPARATION 6

4-(2-Ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide

30 A solution of 2-ethoxybenzoyl chloride (6.1 g, 33.0 mmol) in dichloromethane (50 ml) was added to a stirred solution of 4-amino-1-methyl-3-n-propylpyrazole-5-carboxamide (3.0 g, 16.4 mmol), 4-dimethylaminopyridine (0.02 g, 0.164 mmol) and triethylamine (3.34 g, 33.0 mmol) in dichloromethane (50 ml) at 0°C. The resulting mixture was allowed to warm to room temperature and stirred for a further 2 hours. The solvent was evaporated under vacuum, the residue dissolved in a 19:1 mixture of dichloromethane and methanol (250 ml), and then the solution washed with 1N hydrochloric acid (100 ml), dried ($MgSO_4$) and evaporated under vacuum. The crude material was chromatographed on silica gel (200 g), eluting with a 97:3 mixture of dichloromethane and methanol, to give a pink solid; crystallisation from ethyl acetate-hexane gave the pyrazole-5-carboxamide as a pale pink solid (2.2 g, 40%), m.p. 153-155°C. Found: C, 61.66; H,6.77; N,16.95. $C_{17}H_{22}N_4O_3$ requires C,61.80; H,6.71; N,16.96%.

PREPARATION 7

40 5-(2-Ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

45 4-(2-Ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide (223 g, 0.676 mol) was added portionwise to a solution of sodium hydroxide (54 g, 1.35 mol) and 30% hydrogen peroxide solution (224 ml) in water (2000 ml). Ethanol (700 ml) was added and the resulting mixture heated under reflux for 2.5 hours, cooled, then evaporated under vacuum. The resulting solid was treated with 2N hydrochloric acid (380 ml), with external cooling, and the mixture was extracted with dichloromethane (1 x 700 ml, 3 x 200 ml). The combined organic extracts were washed successively with saturated aqueous sodium carbonate solution (3 x 400 ml) and brine (300 ml), then dried (Na_2SO_4) and evaporated under vacuum.

50 Chromatography of the residue on silica gel (1000 g), using a methanol in dichloromethane elution gradient (0-1% methanol), followed by trituration of the crude product with ether (300 ml), gave the title compound as a colourless solid (152.2 g, 72%), m.p. 143-146°C. Found: C,65.56; H,6.44; N,18.14. $C_{17}H_{20}N_4O_2$ requires C,65.36; H,6.45; N, 17.94%.

PREPARATION 85-(5-Bromoacetyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5 Aluminium trichloride (12.8 g, 0.096 mol) was added portionwise over 1 hour to a stirred solution of 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (10.0 g, 0.032 mol) and bromoacetyl bromide (5.6 ml, 0.064 mol) in dichloromethane (150 ml) at 0°C. After 18 hours at room temperature, the reaction mixture was poured into ice and water (400 g) and the resulting mixture stirred vigorously. The organic phase was separated and the aqueous phase further extracted with dichloromethane (2 x 100 ml). The organic solutions were combined, dried (Na_2SO_4) and evaporated under vacuum to give an off-white solid, trituration of which from ether gave the title compound as a white solid (10.87 g, 78%), m.p. 159-160°C. Found: C, 52.54; H, 4.88; N, 12.78. $\text{C}_{19}\text{H}_{21}\text{BrN}_4\text{O}_3$ requires C, 52.67; H, 4.88; N, 12.93%.

PREPARATION 91-Methyl-4-(2-n-propoxybenzamido)-3-n-propylpyrazole-5-carboxamide

15 This amide was prepared from 2-n-propoxybenzoyl chloride following the procedure described in Preparation 6 and was obtained as a pink solid (63%), m.p. 148-149°C. Found: C, 62.97; H, 7.00; N, 16.29. $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_3$ requires C, 62.77; H, 7.02; N, 16.27%.

PREPARATION 101-Methyl-5-(2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

20 1-Methyl-4-(2-n-propoxybenzamido)-3-n-propylpyrazole-5-carboxamide (0.34 g, 0.99 mmol) was added to a stirred mixture of 30% hydrogen peroxide solution (1.0 ml), potassium carbonate (0.54 g, 3.92 mmol), water (10 ml) and ethanol (5 ml). The mixture was heated under reflux for 38 hours and then evaporated under vacuum. The residue was suspended in water (20 ml), then the suspension acidified with 2N hydrochloric acid and extracted with dichloromethane (3 x 20 ml). The extracts were combined, dried (Na_2SO_4) and evaporated under vacuum. The resulting residue was chromatographed on silica gel (6 g), using a methanol in dichloromethane elution gradient (0-1% methanol), to give an oil, successive trituration of which with ether gave the required product as a white solid (0.19 g, 59%), m.p. 111-114°C. Found: C, 66.26; H, 6.92; N, 17.15. $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_2$ requires C, 66.23; H, 6.80; N, 17.17%.

PREPARATION 115-(5-Bromoacetyl-2-n-propylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

25 Aluminium trichloride (6.0 g, 0.045 mol) was added portionwise to a stirred solution of 1-methyl-5-(2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (5.0 g, 0.0153 mol) and 2-bromoacetyl chloride (2.5 ml, 0.0303 mol) in dichloromethane (100 ml) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for 18 hours, heated under reflux for 3 hours and then added cautiously to ice and water (100 g). The resulting mixture was stirred for 1 hour and extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried (Na_2SO_4), then evaporated under vacuum to give an off-white solid, which was triturated with ether to give the title compound as a white solid (4.1 g, 60%). A small sample was crystallised from ethyl acetate-hexane to give the pure product, m.p. 136-137°C. Found: C, 53.82; H, 5.24; N, 12.57. $\text{C}_{20}\text{H}_{23}\text{BrN}_4\text{O}_3$ requires C, 53.70; H, 5.18; N, 12.52%.

PREPARATION 125-Acetyl-2-ethoxybenzoic acid methyl ester

30 Iodoethane (16.4 g, 0.105 mol) was added to a stirred mixture of 5-acetyl-2-hydroxybenzoic acid methyl ester (10 g, 51.5 mmol) and anhydrous potassium carbonate (14.4 g, 0.104 mol) in 2-butanone (200 ml) and the resulting mixture heated under reflux for 3 days. The solvent was removed by evaporation under vacuum and the residue partitioned between water (100 ml) and ethyl acetate (100 ml). The aqueous phase was removed and extracted with further ethyl acetate (4 x 100 ml). The organic solutions were combined, dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (130 g), using a methanol in dichloromethane elution gradient (0-1% methanol), to

give the title compound as colourless crystals (10.15 g, 89%), m.p. 50-55°C. Found: C,64.88; H,6.38. $C_{12}H_{14}O_4$ requires C,64.85; H,6.35%.

5 PREPARATION 13

5-Acetyl-2-ethoxybenzoic acid

10 A mixture of 5-acetyl-2-ethoxybenzoic acid methyl ester (9.6 g, 0.043 mol), 5M aqueous sodium hydroxide solution (44 ml, 0.217 mol), water (80 ml) and 1,4-dioxan (80 ml) was stirred at room temperature for 18 hours. The solvent was removed by evaporation under vacuum, the residue dissolved in water (100 ml) and the resulting solution acidified to pH 1 with concentrated hydrochloric acid. The aqueous mixture was extracted with ethyl acetate (4 x 100 ml) and the combined extracts dried (Na_2SO_4) and evaporated under vacuum. The resulting solid was crystallised from ethyl acetate to give the title compound as a colourless solid (5.4 g, 60%), m.p. 122-125°C. Found: C,63.20; H,5.81. $C_{11}H_{12}O_4$ requires C,63.45; H,5.81%.

15 PREPARATION 14

5-Acetyl-2-ethoxybenzoyl chloride

20 Oxalyl chloride (3.66 g, 0.029 mol) was added dropwise to a stirred solution of 5-acetyl-2-ethoxybenzoic acid (3.0 g, 0.014 mol) in dichloromethane (15 ml) and dimethylformamide (0.1 ml). After 3 hours at room temperature, the solvent was removed by evaporation under vacuum and the residue azeotroped with hexane (3 x 30 ml) to give the title compound, which was used without further purification.

25 PREPARATION 15

4-(5-Acetyl-2-ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide

30 The title compound was prepared from 5-acetyl-2-ethoxybenzoyl chloride and 4-amino-1-methyl-3-n-propylpyrazole-5-carboxamide following the procedure of Preparation 6, and was obtained as a white solid (60%), m.p. 225-227°C. Found: C,61.35; H,6.25; N,15.07. $C_{19}H_{24}N_4O_4$ requires C,61.28; H,6.50; N,15.04%.

PREPARATION 16

35 5-(5-Chloromethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimdin-7-one

40 1-Methyl-5-(2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.80 g, 0.00246 mol) was added portionwise to stirred concentrated hydrochloric acid (10 ml) at room temperature. Paraformaldehyde (0.20 g, 0.00246 mol) was then added and the resulting solution stirred at 120°C for 22 hours. The reaction mixture was cooled and poured into ice and water (50 g), then the resulting mixture extracted with ethyl acetate (3 x 30 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give a white solid. Trituration with ether, followed by crystallisation from ethyl acetate-hexane, gave the title compound as colourless crystals (0.65 g, 70%), m.p. 102-104°C. Found: C,60.91; H,6.14; N,14.94. $C_{19}H_{23}ClN_4O_2$ requires C,60.88; H,6.18; N,14.95%.

45 PREPARATION 17

5-(2-Ethoxy-5-nitrophenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

50 Concentrated nitric acid (0.5 ml) was added dropwise to a stirred solution of 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (2.0 g, 0.0064 mol) in concentrated sulphuric acid (10 ml) at 0°C, and the resulting orange solution was stirred at room temperature for 18 hours. The reaction solution was then added dropwise to stirred ice and water (200 g) and the solid precipitate collected by filtration. This solid was then dissolved in dichloromethane (50 ml) and the solution washed successively with brine (2 x 30 ml) and water (30 ml), dried (Na_2SO_4) and evaporated under vacuum to give a yellow solid. Crystallisation from acetonitrile gave the title compound as yellow needles (1.40 g, 61%), m.p. 214-216°C. Found: C,57.36; H,5.21; N,19.49. $C_{17}H_{19}N_5O_4$ requires C,57.13; H,5.36; N,19.60%.

PREPARATION 185-(5-Amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5 5-(2-Ethoxy-5-nitrophenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.64 g, 0.0018 mol) was dissolved in ethanol (50 ml) and the solution stirred with 5% palladium on charcoal catalyst (0.050 g) under hydrogen at room temperature and 50 p.s.i. pressure for 4 hours. The mixture was filtered to remove the catalyst, the filtrate evaporated under vacuum, and the residue triturated with ether to give the title compound as an off-white solid (0.56 g, 95%), m.p. 147-148°C. Found: C,62.63; H,6.60; N,21.57. C₁₇H₂₁N₅O₂ requires C,62.36; H,6.47; N,21.39%.

PREPARATION 194-Benzyl-1-piperazinylsulphonyl chloride

15 A solution of 1-benzylpiperazine (20.0 g, 0.114 mol) in acetonitrile (45 ml) was added to a solution of sulphuryl chloride (28 ml, 0.346 mol) in acetonitrile (50 ml) and the mixture heated under reflux for 17 hours, then cooled. The solvent was removed by evaporation under vacuum, then the residue triturated with ether (20 x 50 ml) to yield the title compound (27.8 g, 89%), which was used without further purification.

Biological activity

20 The following Table illustrates the in vitro activities for a range of the compounds of the invention.

TABLE

| EXAMPLE | IC ₅₀ (nM) | | SELECTIVITY RATIO |
|---------|-----------------------|--------|-------------------|
| | cGMP | cAMP | |
| 3 | 2.2 | 86,000 | 39,090 |
| 4 | 1.8 | 63,000 | 35,000 |
| 11 | 4.9 | 57,000 | 11,632 |
| 14 | 1.0 | 57,000 | 57,000 |
| 15 | 3.4 | 75,000 | 22,058 |
| 16 | 3.7 | 53,000 | 14,324 |
| 20 | 3.7 | 59,000 | 15,945 |
| 25 | 3.4 | 84,000 | 24,705 |
| 29 | 5.5 | 84,000 | 15,272 |
| 30 | 1.4 | 58,000 | 41,428 |
| 31 | 3.4 | 56,000 | 16,470 |
| 32 | 1.4 | 38,000 | 27,142 |
| 39 | 5.3 | 54,000 | 10,188 |

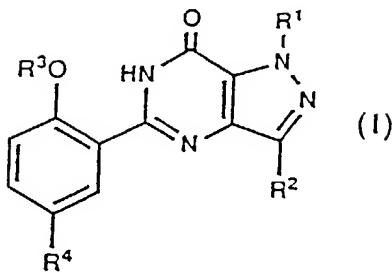
Safety profile

45 Certain compounds of the invention have been tested at therapeutic doses of up to 1 mg/Kg i.v. and up to 3 mg/Kg p.o. in rats with no signs of adverse acute toxicity being observed. In mice, no deaths occurred after doses of up to 100 mg/Kg i.v.

Claims

55 **Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE**

1. A compound of formula:



or a pharmaceutically acceptable salt thereof,
wherein

R¹ is H; C₁-C₃ alkyl optionally substituted with one or more fluoro substituents; or C₃-C₅ cycloalkyl;
R² is H, or C₁-C₆ alkyl optionally substituted with one or more fluoro substituents or with C₃-C₆ cycloalkyl;
R³ is C₁-C₆ alkyl optionally substituted with one or more fluoro substituents or with C₃-C₆ cycloalkyl; C₃-C₅ cycloalkyl; C₃-C₆ alkenyl; or C₃-C₆ alkynyl;
R⁴ is C₁-C₄ alkyl optionally substituted with OH, NR⁵R⁶, CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkenyl optionally substituted with CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkanoyl optionally substituted with NR⁵R⁶; hydroxy C₂-C₄ alkyl optionally substituted with NR⁵R⁶; (C₂-C₃ alkoxy)C₁-C₂ alkyl optionally substituted with OH or NR⁵R⁶; CONR⁵R⁶; CO₂R⁷; halo; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; or phenyl or heterocyclyl either of which is optionally substituted with methyl;
R⁵ and R⁶ are each independently H or C₁-C₄ alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-(NR⁹)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy;
R⁷ H or C₁-C₄ alkyl;
R⁸ is C₁-C₃ alkyl optionally substituted with NR⁵R⁶;
R⁹ H; C₁-C₃ alkyl optionally substituted with phenyl; hydroxy C₂-C₃ alkyl; or C₁-C₄ alkanoyl;

and heterocyclyl means thienyl, pyridyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl or pyrimidinyl.

2. A compound as claimed in claim 1 wherein R¹ is H, methyl or ethyl; R² is C₁-C₃ alkyl; R³ is C₂-C₃ alkyl; R⁴ is C₁-C₂ alkyl optionally substituted with OH, NR⁵R⁶, CONR⁵R⁶ or CO₂R⁷; acetyl optionally substituted with NR⁵R⁶; hydroxyethyl substituted with NR⁵R⁶; ethoxymethyl optionally substituted with OH or NR⁵R⁶; CH=CHCN; CH=CHCONR⁵R⁶; CH=CHCO₂R⁷; CO₂H; CONR⁵R⁶; Br; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R⁵ and R⁶ are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-(NR⁹)-1-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy; R⁷ is H or t-butyl; R⁸ is methyl or CH₂CH₂CH₂NR⁵R⁶; and R⁹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl.
3. A compound as claimed in claim 2 wherein R¹ is methyl; R² is n-propyl; R³ is ethyl or n-propyl; R⁴ is CH₂NR⁵R⁶, CH₂OCH₂CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CO₂H, CONR⁵R⁶, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂NR⁵R⁶, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R⁵ and R⁶ together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-(NR)⁹-1-piperazinyl or 2-methyl-1-imidazolyl group; R⁷ is H or t-butyl; and R⁹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

4. A compound as claimed in claim 3 wherein the said compound is selected from:

5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-acetyl-1-piperazinyl)acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

and pharmaceutically acceptable salts thereof.

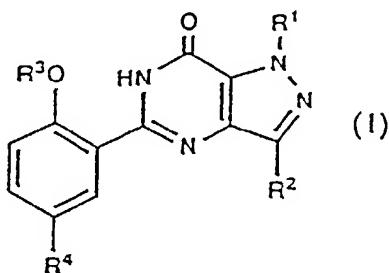
5 5. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, together with a pharmaceutically acceptable diluent or carrier.

10 6. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 5, for use in medicine.

15 7. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 5, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility.

20 **Claims for the following Contracting States : ES, GR**

1. A process for the preparation of a compound of formula:



35 or a pharmaceutically acceptable salt thereof,
wherein

40 R^1 is H; C_1 - C_3 alkyl optionally substituted with one or more fluoro substituents; or C_3 - C_5 cycloalkyl;
 R^2 is H, or C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl;
 R^3 is C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl; C_3 - C_5 cycloalkyl; C_3 - C_6 alkenyl; or C_3 - C_6 alkynyl;
 R^4 is C_1 - C_4 alkyl optionally substituted with OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 alkanoyl optionally substituted with NR^5R^6 ; hydroxy C_2 - C_4 alkyl optionally substituted with NR^5R^6 ; (C_2 - C_3 alkoxy) C_1 - C_2 alkyl optionally substituted with OH or NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halo; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or phenyl or heterocyclyl either of which is optionally substituted with methyl;

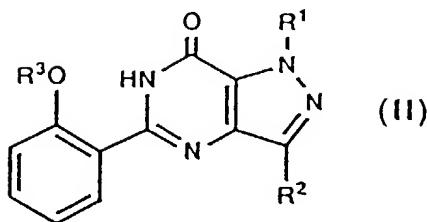
45 R^5 and R^6 are each independently H or C_1 - C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-(NR^9)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy;

R^7 is H or C_1 - C_4 alkyl;

R^8 is C_1 - C_3 alkyl optionally substituted with NR^5R^6 ;

50 R^9 is H; C_1 - C_3 alkyl optionally substituted with phenyl; hydroxy C_2 - C_3 alkyl; or C_1 - C_4 alkanoyl;

55 and heterocyclyl means thienyl, pyridyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl or pyrimidinyl; which comprises reacting a compound of formula (II):



wherein R¹, R² and R³ are as previously defined in this claim, for a compound of formula (I) when R⁴ is

(A) C₂-C₄ alkanoyl or hydroxy C₂-C₄ alkyl,

with an acyl halide of formula (C₁-C₃ alkyl)COY wherein Y is halo, in the presence of a Lewis acid, optionally followed by reduction of the resulting ketone to the corresponding alcohol;

(B) C₂-C₄ alkanoyl or hydroxy C₂-C₄ alkyl, each substituted with NR⁵R⁶ wherein R⁵ and R⁶ are as previously defined in this claim,

with a haloacyl halide of formula X(C₁-C₃ alkylene)COY wherein X is halo and Y is as previously defined in this claim, in the presence of a Lewis acid, followed by reaction of the resulting halo ketone either with an amine of formula R⁵R⁶NH, optionally followed by reduction of the resulting aminoketone, or with a protected amine of formula R⁵NHP, R⁶NHP or P'₂NH wherein P and P' are suitable amine protecting groups, optionally followed by reduction of the resulting aminoketone before or after removal of P or P';

(C) C₁-C₄ alkyl optionally substituted with OH, NR⁵R⁶, CONR⁵R⁶ or CO₂R⁷ wherein R⁵, R⁶ and R⁷ are as previously defined in this claim, or bromo,

(i) under chloromethylation conditions, followed by subjection of the resulting chloromethyl intermediate to, respectively,

(a) reduction, or

(b) reaction with an alkali metal hydroxide, or

(c) reaction with an amine of formula R⁵R⁶NH, or

(d) reaction with an alkali metal cyanide and optionally converting the resulting nitrile to the corresponding amide, acid or ester; or

(ii) under aromatic bromination conditions, followed by subjection of the resulting bromo derivative to, respectively,

(a) lithium-bromine exchange, followed by reaction of the aryllithium derivative with ethylene oxide to give the 2-hydroxyethyl derivative, or

(b) reaction with allyl alcohol, followed by catalytic hydrogenation of the alkene to give the 3-hydroxypropyl derivative, or (c) reaction with 3-buten-1-ol, followed by catalytic hydrogenation of the alkene to give the 4-hydroxybutyl derivative,

and optional conversion of any of the foregoing alcohols to the corresponding alkane, amine or nitrile by activation of their respective hydroxy groups to give the chloride or mesylate followed by reduction, or reaction with an amine of formula R⁵R⁶NH, or reaction with an alkali metal cyanide, respectively, and further optional conversion of the said nitrile to the corresponding amide or ester;

(D) C₂-C₄ alkenyl 2-substituted with CN, CONR⁵R⁶ or CO₂R⁷, or C₂-C₄ alkyl 2-substituted with CN, CONR⁵R⁶, CO₂R⁷ or CH₂NH₂, wherein R⁵, R⁶ and R⁷ are as previously defined in this claim,

via the bromo derivative of (C) (ii) above, with the appropriate α , β -unsaturated nitrile, amide or ester respectively, optionally followed by hydrolysis of any resulting ester, reduction of the resulting alkenyl group and, in the case of the nitrile, further or concomitant reduction of the nitrile group to the corresponding primary amine;

(E) C₂-C₄ alkenyl, or C₂-C₄ alkyl, each optionally substituted with CN, CONR⁵R⁶ or CO₂R⁷ wherein R⁵, R⁶ and

5 R^7 are as previously defined in this claim,
via the bromo derivative of (C) (ii) above, with a lithium-bromine exchange reagent, followed by subjection of the aryllithium derivative to formylation, and reaction of the resulting aldehyde with the appropriate optionally CN-, CONR⁵R⁶- or CO₂R⁷-substituted C₁-C₃ alkyl phosphonium salt or phosphonate, optionally followed by hydrolysis of any resulting ester and reduction of the resulting alkenyl group;

10 (F) (C₂-C₃ alkoxy)C₁-C₂ alkyl optionally substituted with OH or NR⁵R⁶ wherein R⁵ and R⁶ are as previously defined in this claim,

15 (i) via the chloromethyl derivative of (C) (i) above, with either

(a) a C₂- or C₃-alkanol, or

(b) a C₂- or C₃-diol, optionally followed by activation of the hydroxy group to give the mesylate and reaction either with an amine of formula R⁵R⁶NH, or with a protected amine of formula R⁵NHP, R⁶NHP or P'₂NH wherein P and P' are as previously defined in this claim; or

20 (ii) via the bromo derivative of (C) (ii) above, with a lithium-bromine exchange reagent, followed by reaction of the aryllithium derivative with ethylene oxide to give the 2-hydroxyethyl derivative, and activation of the hydroxy group and further reaction as in (i)(a) or (i)(b);

25 (G) CONR⁵R⁶ or CO₂R⁷ wherein R⁵, R⁶ and R⁷ are as previously defined in this claim,

via the bromo derivative of (C) (ii) above, with a lithium-bromine exchange reagent, followed by reaction of the aryllithium derivative with carbon dioxide, and conversion of a suitably activated form of the resulting carboxylic acid to an amide or ester derivative by reaction with an amine of formula R⁵R⁶NH or alcohol of formula R⁷OH respectively ;

30 (H) NH₂, halo, NSO₂NR⁵R⁶ or NSO₂R⁸ wherein halo is fluoro, chloro, bromo or iodo, and R⁵, R⁶ and R⁸ are as previously defined in this claim,

under aromatic nitration conditions, followed by reduction of the resulting nitro compound to the corresponding primary amine, and subjection of the said amine to, respectively,

35 (a) a conventional diazotisation-halogenation reaction sequence, or

(b) reaction with either a sulphonamoyl halide of formula R⁵R⁶NSO₂halo or a sulphonyl halide of formula R⁸SO₂halo, wherein halo is preferably chloro, or reaction with sulphonamide when both R⁵ and R⁶ are H;

40 (I) phenyl or heterocyclyl, either of which is optionally substituted with methyl,

via the bromo derivative of (C) (ii) above, with either

(i) when R⁴ is optionally substituted phenyl or C-linked heterocyclyl, the appropriate optionally substituted phenyl or heterocyclyl zincate derivative in the presence of a palladium catalyst, or

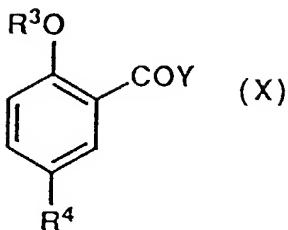
(ii) when R⁴ is N-linked heterocycle, the appropriate heterocycle in the presence of copper-bronze, iodine and a base;

45 followed in each case, by optional isolation as, or formation of, a pharmaceutically acceptable salt of the product.

50 2. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³ and R⁴ are as previously defined in claim 1, which comprises reacting a compound of formula (II), wherein R³ is H and R¹ and R² are as previously defined in claim 1, according to any process defined in claim 1 followed by O-alkylation of the phenolic group to introduce R³ and optional isolation as, or formation of, a pharmaceutically acceptable salt of the product.

55 3. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³ and R⁴ are as previously defined in claim 1, which comprises reacting a compound of formula (X):

5

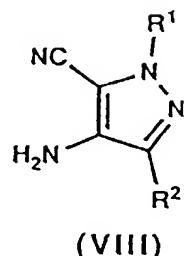
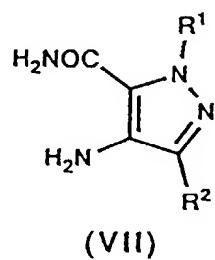


10

wherein Y is chloro or bromo, and R³ and R⁴ are as previously defined in claim 1, with an aminopyrazole of either formula (VII) or formula (VIII):

15

20



25

wherein R¹ and R² are as previously defined in claim 1, followed by cyclisation of the respective resulting amides by treatment with a base, optionally in the presence of hydrogen peroxide, and optional isolation as, or formation of, a pharmaceutically acceptable salt.

30

4. A process as claimed in claim 1 wherein

in (A), Y is chloro or bromo, the Lewis acid is aluminium chloride or aluminium bromide, and the reducing agent is sodium borohydride;

35

in (B), X and Y are chloro or bromo, P is benzyl and is removed by catalytic hydrogenation, and P' is t-butoxycarbonyl and is removed using hydrogen chloride;

40

in (C),

(i) the chloromethylation is carried out using paraformaldehyde and concentrated hydrochloric acid, and

- (a) the reduction is effected by palladium-catalysed hydrogenation,
- (b) the alkali metal hydroxide is sodium hydroxide or potassium hydroxide,
- (c) the reaction with R⁵R⁶NH is carried out using an excess of said amine,
- (d) the alkali metal cyanide is sodium cyanide or potassium cyanide;

(ii) the aromatic bromination is carried out using N-bromosuccinimide, and

- (a) the lithium-bromine exchange is effected using n-butyllithium,
- (b) the reaction with allyl alcohol is effected under Heck reaction conditions,
- (c) the reaction with 3-buten-1-ol is effected under Heck reaction conditions;

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50

in (D), the reaction with the appropriate α,β -unsaturated nitrile, amide or ester respectively, is effected under Heck reaction conditions using tri-*o*-tolylphosphine, palladium(II) acetate and triethylamine, the optional hydrolysis of the ester is achieved using aqueous sodium hydroxide solution in methanol, the optional reduction of the alkenyl group is effected by palladium-catalysed hydrogenation, and the optional further or concomitant reduction of the nitrile group is carried out using Raney nickel in glacial acetic acid;

in (E), the lithium-bromine exchange is effected using n-butyllithium, the formylation reagent is dimethylformamide, and the alkene reduction is achieved by catalytic hydrogenation;

5 in (F), the reaction with

(a) a C₂- or C₃-alkanol, is carried out in the presence of one equivalent of sodium metal, or

10 (b) a C₂- or C₃-diol, is carried out in the presence of one equivalent of sodium metal, the hydroxy group is converted to its mesylate using mesyl chloride in pyridine as solvent, and the reaction with R⁵R⁶NH is carried out using an excess of said amine; and

15 (ii) the lithium-bromine exchange is effected using n-butyllithium;

in (G), the lithium-bromine exchange is effected using n-butyllithium, and the carboxylic acid is activated using a carbodiimide in combination with 1-hydroxybenzotriazole;

15 in (H), the nitration is achieved using concentrated nitric acid in combination with concentrated sulphuric acid, the nitro compound is reduced by catalytic hydrogenation, the reaction with a sulphanoyl chloride or with a sulphonyl chloride is carried out in the presence of excess pyridine or triethylamine optionally in the presence of 4-dimethylaminopyridine, and the reaction with sulphanide is effected at about 100°C;

20 in (I),

25 (i) the palladium catalyst is tetrakis(triphenylphosphine)palladium(0), and the optionally substituted phenyl or heterocycl zincate derivative is obtained from the corresponding optionally substituted phenyl or heterocyclolithium derivative and anhydrous zinc chloride; and

(ii) the heterocyclic is present in excess, and the base is anhydrous potassium carbonate.

- 30 5. A process as claimed in claim 2 wherein the O-alkylation is effected using the appropriate alkyl chloride, bromide or sulphonate, in the presence of potassium carbonate.
- 35 6. A process as claimed in any one of claims 1 to 5 wherein R¹ is H, methyl or ethyl; R² is C₁-C₃ alkyl; R³ is C₂-C₃ alkyl; R⁴ is C₁-C₂ alkyl optionally substituted with OH, NR⁵R⁶, CONR⁵R⁶ or CO₂R⁷; acetyl optionally substituted with NR⁵R⁶; hydroxyethyl substituted with NR⁵R⁶; ethoxymethyl optionally substituted with OH or NR⁵R⁶; CH=CH-CN; CH=CHCONR⁵R⁶; CH=CHCO₂R⁷; CO₂H; CONR⁵R⁶; Br; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R⁵ and R⁶ are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-(NR⁹)-1-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy; R⁷ is H or t-butyl; R⁸ is methyl or CH₂CH₂CH₂NR⁵R⁶; and R⁹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl.
- 40 7. A process as claimed in claim 6 wherein R¹ is methyl; R² is n-propyl; R³ is ethyl or n-propyl; R⁴ is CH₂NR⁵R⁶, CH₂OCH₂CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CO₂H, CONR⁵R⁶, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂CH₂NR⁵R⁶, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R⁵ and R⁶ together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-(NR⁹)-1-piperazinyl or 2-methyl-1-imidazolyl group; R⁷ is H or t-butyl; and R⁹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl.
- 45 8. A process as claimed in claim 7 wherein said compound of formula (I) produced is selected from:

50 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
 5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
 5-[5-(4-acetyl-1-piperazinyl)acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and pharmaceutically acceptable salts thereof.

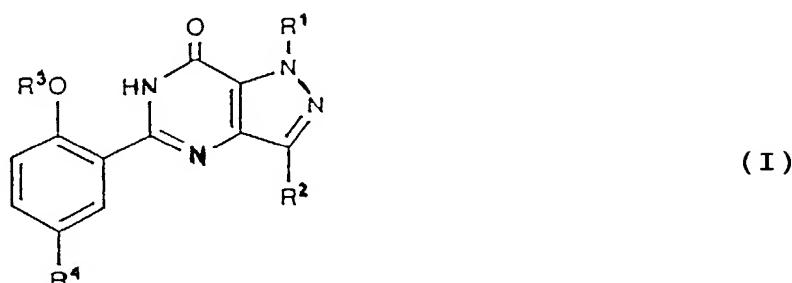
Patentansprüche

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Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

10 1. Verbindung der Formel:

10



25 oder ein pharmazeutisch annehmbares Salz hievon, worin R¹ H; C₁-C₃-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten; oder C₃-C₅-Cycloalkyl bedeutet; R² H oder C₁-C₆-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C₃-C₆-Cycloalkyl, darstellt; R³ C₁-C₆-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C₃-C₆-Cycloalkyl; C₃-C₅-Cycloalkyl; C₃-C₆-Alkenyl oder C₃-C₆-Alkinyl ist; R⁴ C₁-C₄-Alkyl, gegebenenfalls substituiert mit OH, NR⁵R⁶, CN, CONR⁵R⁶ oder CO₂R⁷; C₂-C₄-Alkenyl, gegebenenfalls substituiert mit CN, CONR⁵R⁶ oder CO₂R⁷; C₂-C₄-Alkanoyl, gegebenenfalls substituiert mit NR⁵R⁶; Hydroxy-C₂-C₄-alkyl, gegebenenfalls substituiert mit NR⁵R⁶; (C₂-C₃-Alkoxy)-C₁-C₂-alkyl, gegebenenfalls substituiert mit OH oder NR⁵R⁶; CONR⁵R⁶; CO₂R⁷; Halogen; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; oder Phenyl oder Heterocyclyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, bedeutet; R⁵ und R⁶ jeweils unabhängig H oder C₁-C₄-Alkyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-(NR⁹)-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R⁷ H oder C₁-C₄-Alkyl bedeutet; R⁸ C₁-C₃-Alkyl, gegebenenfalls substituiert mit NR⁵R⁶, darstellt; R⁹ H, C₁-C₃-Alkyl, gegebenenfalls substituiert mit Phenyl; Hydroxy-C₂-C₃-alkyl oder C₁-C₄-Alkanoyl ist; und Heterocyclyl Thienyl, Pyridyl, Pyrazolyl, Imidazolyl, Triazolyl, Oxazolyl, Thiazolyl oder Pyrimidinyl bedeutet.

40 2. Verbindung nach Anspruch 1, worin R¹ H, Methyl oder Ethyl bedeutet; R² C₁-C₃-Alkyl darstellt; R³ C₂-C₃-Alkyl ist;

R⁴ C₁-C₂-Alkyl, gegebenenfalls substituiert mit OH, NR⁵R⁶, CONR⁵R⁶ oder CO₂R⁷; Acetyl, gegebenenfalls substituiert mit NR⁵R⁶; Hydroxyethyl, substituiert mit NR⁵R⁶; Ethoxymethyl, gegebenenfalls substituiert mit OH oder NR⁵R⁶; CH=CHCN; CH=CHCONR⁵R⁶; CH=CHCO₂R⁷; CO₂H; CONR⁵R⁶; Br; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; oder Pyridyl oder Imidazolyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, bedeutet; R⁵ und R⁶ jeweils unabhängig H, Methyl oder Ethyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, Morpholino-, 4-(NR⁹)-1-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R⁷ H oder tert. Butyl bedeutet; R⁸ Methyl oder CH₂CH₂CH₂NR⁵R⁶ darstellt; und R⁹ H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl bedeutet.

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50 3. Verbindung nach Anspruch 2, worin R¹ Methyl bedeutet; R² n-Propyl darstellt; R³ Ethyl oder n-Propyl ist; R⁴ CH₂NR⁵R⁶, CH₂OCH₂CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CO₂H, CONR⁵R⁶, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂CH₂NR⁵R⁶, 2-Pyridyl, 1-Imidazolyl oder 1-Methyl-2-imidazolyl bedeutet; R⁵ und R⁶ zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, 4-Hydroxypiperidino-, Morpholino-, 4-(NR⁹)-1-Piperazinyl- oder 2-Methyl-1-imidazolyl-Gruppe bilden; R⁷ H oder tert. Butyl bedeutet; und R⁹ H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt.

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4. Verbindung nach Anspruch 3, wobei diese Verbindung ausgewählt ist aus:

5-[2-Ethoxy-5-(1-methyl-2-imidazolyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;

5-[2-Ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;

5-[5-(4-Acetyl-1-piperazinyl)-acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;

5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on; und

10 5-(5-Morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on,

und pharmazeutisch annehmbaren Salzen hievon.

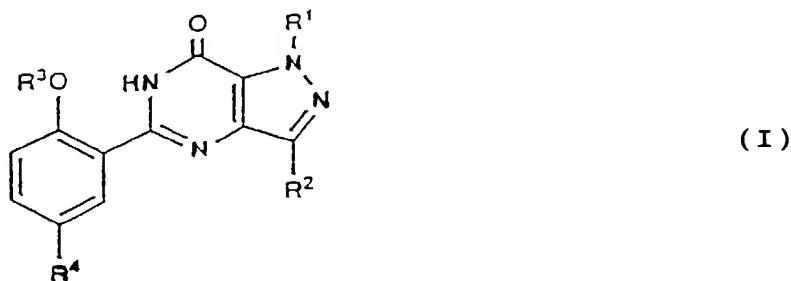
5. Pharmazeutische Zusammensetzung, welche eine Verbindung der Formel (I), oder ein pharmazeutisch annehmbares Salz hievon, nach einem der Ansprüche 1 bis 4 zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger umfaßt.

15 6. Verbindung der Formel (I), oder ein pharmazeutisch annehmbares Salz hievon, oder eine pharmazeutische Zusammensetzung, die eine der Einheiten enthält, nach einem der Ansprüche 1 bis 5 zur Verwendung in der Medizin.

20 7. Verwendung einer Verbindung der Formel (I), oder eines pharmazeutisch annehmbaren Salzes hievon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, nach einem der Ansprüche 1 bis 5 bei der Herstellung eines Medikaments zur Behandlung von stabiler, instabiler und Variant-(Prinzmetal-) Angina, Hypertension, pulmonaler Hypertension, kongestivem Herzversagen, Atherosklerose, Schlaganfall, peripheren Gefäßerkrankungen, Zuständen einer verringerten Durchgängigkeit der Blutgefäße, chromischem Asthma, Bronchitis, allergischem Asthma, allergischer Rhinitis, Glaukom oder durch Störungen der Darmmotilität charakterisierten Erkrankungen.

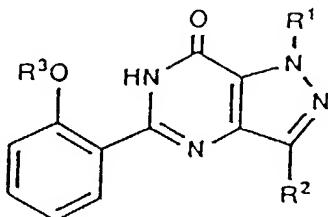
30 Patentansprüche für folgende Vertragsstaaten : ES, GR

35 1. Verfahren zur Herstellung einer Verbindung der Formel:



oder eines pharmazeutisch annehmbaren Salzes hievon, worin R¹ H; C₁-C₃-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten; oder C₃-C₅-Cycloalkyl bedeutet; R² H oder C₁-C₆-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C₃-C₆-Cycloalkyl, darstellt; R³ C₁-C₆-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C₃-C₆-Cycloalkyl; C₃-C₅-Cycloalkyl, C₃-C₆-Alkenyl oder C₃-C₆-Alkinyl ist; R⁴ C₁-C₄-Alkyl, gegebenenfalls substituiert mit OH, NR⁵R⁶, CN, CONR⁵R⁶ oder CO₂R⁷; C₂-C₄-Alkenyl, gegebenenfalls substituiert mit CN, CONR⁵R⁶ oder CO₂R⁷; C₂-C₄-Alkanoyl, gegebenenfalls substituiert mit NR⁵R⁶; Hydroxy-C₂-C₄-alkyl, gegebenenfalls substituiert mit NR⁵R⁶; (C₂-C₃-Alkoxy)-C₁-C₂-alkyl, gegebenenfalls substituiert mit OH oder NR⁵R⁶; CONR⁵R⁶; CO₂R⁷; Halogen; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; oder Phenyl oder Heterocyclyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, bedeutet; R⁵ und R⁶ jeweils unabhängig H oder C₁-C₄-Alkyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-(NR⁹)-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R⁷ H oder C₁-C₄-Alkyl bedeutet; R⁸ C₁-C₃-Alkyl, gegebenenfalls substituiert mit NR⁵R⁶, darstellt; R⁹ H; C₁-C₃-Alkyl, gegebenenfalls substituiert mit Phenyl; Hydroxy-C₂-C₃-alkyl oder C₁-C₄-Alkanoyl ist; und Heterocyclyl Thienyl, Pyridyl,

Pyrazolyl, Imidazolyl, Triazolyl, Oxazolyl, Thiazolyl oder Pyrimidinyl bedeutet; welches Verfahren umfaßt: Umsetzen einer Verbindung der Formel (II):



15 worin R¹, R² und R³ wie vorstehend in diesem Anspruch für eine Verbindung der Formel (I) definiert sind, wenn R⁴ bedeutet:

(A) C₂-C₄-Alkanoyl oder Hydroxy-C₂-C₄-alkyl, mit einem Acylhalogenid der Formel (C₁-C₃-Alkyl)COY, wobei Y Halogen darstellt, in Anwesenheit einer Lewis-Säure, gegebenenfalls gefolgt von einer Reduktion des erhaltenen Ketons zum entsprechenden Alkohol;

(B) C₂-C₄-Alkanoyl oder Hydroxy-C₂-C₄-alkyl, jeweils substituiert mit NR⁵R⁶, wobei R⁵ und R⁶ wie vorstehend in diesem Anspruch definiert sind, mit einem Halogenacylhalogenid der Formel X(C₁-C₃-Alkylen)COY, wobei X Halogen darstellt, und Y wie vorstehend in diesem Anspruch definiert ist, in Anwesenheit einer Lewis-Säure, gefolgt vom Umsetzen des erhaltenen Halogenketons entweder mit einem Amin der Formel R⁵R⁶NH, gegebenenfalls gefolgt von der Reduktion des erhaltenen Aminoketons, oder mit einem geschützten Amin der Formel R⁵NHP, R⁶NHP oder P¹₂NH, wobei P und P¹ geeignete Amin-Schutzgruppen sind, gegebenenfalls gefolgt von der Reduktion des erhaltenen Aminoketons vor oder nach der Entfernung von P oder P¹;

(C) C₁-C₄-Alkyl, gegebenenfalls substituiert mit OH, NR⁵R⁶, CONR⁵R⁶ oder CO₂R⁷, wobei R⁵, R⁶ und R⁷ wie vorstehend in diesem Anspruch definiert sind, oder Brom,

30 (i) unter Chlormethylierungsbedingungen, gefolgt vom Unterwerfen der erhaltenen Chlormethyl-Zwischenverbindung jeweils

35 (a) einer Reduktion, oder

(b) einem Umsetzen mit einem Alkalimetallhydroxid, oder

(c) einem Umsetzen mit einem Amin der Formel R⁵R⁶NH, oder

40 (d) einem Umsetzen mit einem Alkalimetallcyanid, und gegebenenfalls einem Überführen des erhaltenen Nitrils in das entsprechende Amid, die Säure oder den Ester; oder

(ii) unter aromatischen Bromierungsbedingungen, gefolgt vom Unterwerfen des erhaltenen Brom-Derivats jeweils

45 (a) einem Lithium-Brom-Austausch, gefolgt vom Umsetzen des Aryllithium-Derivats mit Ethylenoxid, wobei das 2-Hydroxyethyl-Derivat erhalten wird, oder

(b) einem Umsetzen mit Allylalkohol, gefolgt von katalytischer Hydrierung des Alkens, wobei das 3-Hydroxypropyl-Derivat erhalten wird, oder

50 (c) einem Umsetzen mit 3-Buten-1-ol, gefolgt von katalytischer Hydrierung des Alkens, wobei das 4-Hydroxybutyl-Derivat erhalten wird, und gegebenenfalls Überführen irgendeines der vorstehenden Alkohole in das entsprechende Alkan, Amin oder Nitril durch die Aktivierung ihrer entsprechenden Hydroxy-Gruppen, wobei das Chlorid oder Mesylat erhalten wird, gefolgt von einer Reduktion, oder einem Umsetzen mit einem Amin der Formel R⁵R⁶NH, bzw. einem Umsetzen mit einem Alkalimetallcyanid und einer weiteren gegebenenfalls durchgeführten Überführung des Nitrils in das entsprechende Amid oder den Ester;

55 (D) C₂-C₄-Alkenyl, 2-substituiert mit CN, CONR⁵R⁶ oder CO₂R⁷, oder C₂-C₄-Alkyl, 2-substituiert mit CN, CONR⁵R⁶, CO₂R⁷ oder CH₂NH₂, wobei R⁵, R⁶ und R⁷ wie vorstehend in diesem Anspruch definiert sind, über das Brom-Derivat von (C)(ii) oben, mit dem geeigneten α,β -ungesättigten Nitril, Amid bzw. Ester, gegebenenfalls gefolgt von einer Hydrolyse irgendeines erhaltenen Esters, Reduktion der erhaltenen Alkenyl-Gruppe und, im Fall des Nitrils, weiterer oder gleichzeitiger Reduktion der Nitril-Gruppe zum entsprechenden primären

5 Amin;

(E) C₂-C₄-Alkenyl oder C₂-C₄-Alkyl, jeweils gegebenenfalls substituiert mit CN, CONR⁵R⁶ oder CO₂R⁷, wobei R⁵, R⁶ und R⁷ wie vorstehend in diesem Anspruch definiert sind, über das Brom-Derivat von (C)(ii) oben, mit einem Lithium-Brom-Austauschreagens, gefolgt vom Unterwerfen des Aryllithium-Derivats einer Formylie-
10 rung, und Umsetzen des erhaltenen Aldehyds mit dem geeigneten, gegebenenfalls CN-, CONR⁵R⁶- oder CO₂R⁷-substituierten, C₁-C₃-Alkylphosphoniumsalz oder Phosponat, gegebenenfalls gefolgt von einer Hy-
drolyse irgendeines erhaltenen Esters und Reduktion der erhaltenen Alkenyl-Gruppe;
15 (F) (C₂-C₃-Alkoxy)-C₁-C₂-alkyl, gegebenenfalls substituiert mit OH oder NR⁵R⁶, wobei R⁵ und R⁶ wie vorste-
hend in diesem Anspruch definiert sind,

10 (i) über das Chlormethyl-Derivat von (C)(i) oben, entweder mit

- 15 (a) einem C₂- oder C₃-Alkanol oder
- (b) einem C₂- oder C₃-Diol, gegebenenfalls gefolgt von einer Aktivierung der Hydroxy-Gruppe, wobei das Mesylat erhalten wird, und einem Umsetzen entweder mit einem Amin der Formel R⁵R⁶NH oder mit einem geschützten Amin der Formel R⁵NHP, R⁶NHP oder P'₂NH, wobei P und P' wie vorstehend in diesem Anspruch definiert sind; oder

20 (ii) über das Brom-Derivat von (C)(ii) oben, mit einem Lithium-Brom-Austauschreagens, gefolgt von einem Umsetzen des Aryllithium-Derivats mit Ethylenoxid, wobei das 2-Hydroxyethyl-Derivat erhalten wird, und einer Aktivierung der Hydroxy-Gruppe und einem weiteren Umsetzen wie in (i)(a) oder (i)(b);

25 (G) CONR⁵R⁶ oder CO₂R⁷, wobei R⁵, R⁶ und R⁷ wie vorstehend in diesem Anspruch definiert sind, über das Brom-Derivat von (C)(ii) oben, mit einem Lithium-Brom-Austauschreagens, gefolgt von einem Umsetzen des Aryllithium-Derivats mit Kohlendioxid, und Überführen einer geeignet aktivierten Form der erhaltenen Carbonsäure in ein Amid- oder Ester-Derivat durch das Umsetzen mit einem Amin der Formel R⁵R⁶NH bzw. Alkohol der Formel R⁷OH;

30 (H) NH₂, Halogen, NHSO₂NR⁵R⁶ oder NHSO₂R⁸, wobei Halogen Fluor, Chlor, Brom oder Iod bedeutet, und R⁵, R⁶ und R⁸ wie vorstehend in diesem Anspruch definiert sind, unter aromatischen Nitrierungsbedingungen, gefolgt von einer Reduktion der erhaltenen Nitro-Verbindung zum entsprechenden primären Amin, und Unterwerfen des Amins jeweils

- 35 (a) einer herkömmlichen Diazotierungs-Halogenierungs-Sequenz, oder
- (b) einem Umsetzen entweder mit einem Sulfamoylhalogenid der Formel R⁵R⁶NSO₂Halogen oder einem Sulfonylhalogenid der Formel R⁸SO₂Halogen, wobei Halogen vorzugsweise Chlor bedeutet, oder einem Umsetzen mit Sulfamid, wenn sowohl R⁵ als auch R⁶ H darstellen;

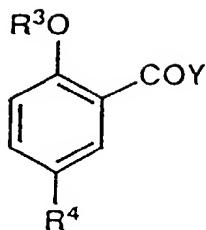
40 (I) Phenyl oder Heterocycl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, über das Brom-Derivat von (C)(ii) oben, entweder mit

- 45 (i) wenn R⁴ gegebenenfalls substituiertes Phenyl oder C-gebundenes Heterocycl ist, dem geeigneten, gegebenenfalls substituierten, Phenyl- oder Heterocyclzinkat-Derivat in Anwesenheit eines Palladium-Katalysators, oder
- (ii) wenn R⁴ ein N-gebundener Heterocyclus ist, dem geeigneten Heterocyclus in Anwesenheit von Kupfer-Bronze, Iod und einer Base;

50 gefolgt in jedem Fall von der gegebenenfalls durchgeführten Isolierung als pharmazeutisch annehmbares Salz des Produkts oder Bildung desselben.

- 55 2. Verfahren zur Herstellung einer Verbindung der Formel (I), oder eines pharmazeutisch annehmbaren Salzes hie- von, worin R¹, R², R³ und R⁴ wie vorstehend in Anspruch 1 definiert sind, welches umfaßt: Umsetzen einer Ver- bindung der Formel (II), worin R³ die Bedeutung H hat, und R¹ und R² wie vorstehend in Anspruch 1 definiert sind, gemäß einem beliebigen in Anspruch 1 definierten Verfahren, gefolgt von einer O-Alkylierung der Phenol-Gruppe zur Einführung von R³ und der gegebenenfalls durchgeführten Isolierung eines pharmazeutisch annehmbaren Salzes des Produkts oder Bildung desselben.
3. Verfahren zur Herstellung einer Verbindung der Formel (I), oder eines pharmazeutisch annehmbaren Salzes hie- von, worin R¹, R², R³ und R⁴ wie vorstehend in Anspruch 1 definiert sind, welches umfaßt: Umsetzen einer Ver-

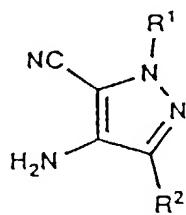
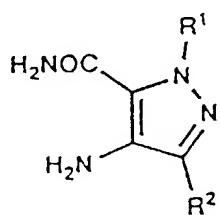
bindung der Formel (X):



(X),

15

worin Y Chlor oder Brom bedeutet, und R³ und R⁴ wie vorstehend in Anspruch 1 definiert sind, mit einem Aminopyrazol entweder der Formel (VII) oder der Formel (VIII):



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worin R¹ und R² wie vorstehend in Anspruch 1 definiert sind, gefolgt von der Cyclisierung der entsprechenden erhaltenen Amide durch die Behandlung mit einer Base, gegebenenfalls in Anwesenheit von Wasserstoffperoxid, und der gegebenenfalls durchgeföhrten Isolierung als pharmazeutisch annehmbares Salz oder Bildung desselben.

4. Verfahren nach Anspruch 1, wobei

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in (A) Y Chlor oder Brom bedeutet, die Lewis-Säure Aluminiumchlorid oder Aluminiumbromid ist, und das Reduktionsmittel Natriumborhydrid ist;

in (B) X und Y Chlor oder Brom bedeuten, P Benzyl darstellt und durch katalytische Hydrierung entfernt wird, und P' tert.Butoxycarbonyl ist und unter Verwendung von Chlorwasserstoff entfernt wird;

in (C)

40

(i) die Chlormethylierung unter Verwendung von Paraformaldehyd und konzentrierter Salzsäure durchgeführt wird, und

45

(a) die Reduktion durch Palladium-katalysierte Hydrierung bewirkt wird,

(b) das Alkalimetallhydroxid Natriumhydroxid oder Kaliumhydroxid ist,

(c) das Umsetzen mit R⁵R⁶NH unter Verwendung eines Überschusses des Amins durchgeföhrert wird,

(d) das Alkalimetallcyanid Natriumcyanid oder Kaliumcyanid ist;

50

(ii) die aromatische Bromierung unter Verwendung von N-Bromsuccinimid durchgeföhrert wird, und

(a) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium bewirkt wird,

(b) das Umsetzen mit Allylalkohol unter Heck-Reaktionsbedingungen durchgeföhrert wird,

(c) das Umsetzen mit 3-Buten-1-ol unter Heck-Reaktionsbedingungen bewirkt wird;

55

in (D) das Umsetzen mit dem geeigneten α,β -ungesättigten Nitril, Amid bzw. Ester unter Heck-Reaktionsbedingungen unter Verwendung von Tri-*o*-tolylphosphin, Palladium(II)-acetat und Triethylamin durchgeföhrert wird, die gegebenenfalls vorgenommene Hydrolyse des Esters unter Verwendung wässriger Natriumhydroxid-Lösung in Methanol erzielt wird, die gegebenenfalls durchgeföhrte Reduktion der Alkenyl-Gruppe durch Palladium-katalysierte Hydrierung bewirkt wird, und die gegebenenfalls vorgenommene weitere oder gleichzeitige

Reduktion der Nitril-Gruppe unter Verwendung von Raney-Nickel in Eisessig durchgeführt wird; in (E) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium durchgeführt wird, das Formylierungsreagens Dimethylformamid ist, und die Alken-Reduktion durch katalytische Hydrierung erzielt wird; in (F) das Umsetzen mit

5 (a) einem C₂- oder C₃-Alkanol in Anwesenheit von einem Äquivalent Natriummetall durchgeführt wird, oder
 (b) einem C₂- oder C₃-Diol in Anwesenheit von einem Äquivalent Natriummetall durchgeführt wird, die Hydroxy-Gruppe unter Verwendung von Mesylchlorid in Pyridin als Lösungsmittel in ihr Mesylat übergeführt wird, und das Umsetzen mit R⁵R⁶NH unter Verwendung eines Überschusses des Amins durchgeführt wird; und
 10 (ii) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium durchgeführt wird;

15 in (G) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium durchgeführt wird, und die Carbonsäure unter Verwendung eines Carbodiimids in Kombination mit 1-Hydroxybenzotriazol aktiviert wird;

20 in (H) die Nitrierung unter Verwendung konzentrierter Salpetersäure in Kombination mit konzentrierter Schwefelsäure erzielt wird, die Nitro-Verbindung durch katalytische Hydrierung reduziert wird, das Umsetzen mit einem Sulfamoylchlorid oder mit einem Sulfonylchlorid in Anwesenheit eines Pyridin- oder Triethylamin-Überschusses, gegebenenfalls in Anwesenheit von 4-Dimethylaminopyridin, durchgeführt wird, und das Umsetzen mit Sulfamid bei etwa 100°C bewirkt wird;

25 in (I) der Palladium-Katalysator Tetrakis-(triphenylphosphin)-palladium(0) ist, und das gegebenenfalls substituierte Phenyl- oder Heterocyclzyinkat-Derivat aus dem entsprechenden gegebenenfalls substituierten Phenyl- oder Heterocyclolithium-Derivat und wasserfreiem Zinkchlorid erhalten wird; und
 (ii) der Heterocyclus im Überschuß vorhanden ist, und die Base wasserfreies Kaliumcarbonat ist.

25 5. Verfahren nach Anspruch 2, bei welchem die O-Alkylierung unter Verwendung des geeigneten Alkylchlorids, Bro-
 mids oder Sulfonats in Anwesenheit von Kaliumcarbonat durchgeführt wird.

30 6. Verfahren nach einem der Ansprüche 1 bis 5, wobei R¹ H, Methyl oder Ethyl bedeutet; R² C₁-C₃-Alkyl darstellt; R³ C₂-C₃-Alkyl ist; R⁴ C₁-C₂-Alkyl, gegebenenfalls substituiert mit OH, NR⁵R⁶, CONR⁵R⁶ oder CO₂R⁷; Acetyl, gegebenenfalls substituiert mit NR⁵R⁶; Hydroxyethyl, substituiert mit NR⁵R⁶; Ethoxymethyl, gegebenenfalls substituiert mit OH oder NR⁵R⁶; CH=CHCN; CH=CHCONR⁵R⁶; CH=CHCO₂R⁷; CO₂H; CONR⁵R⁶; Br; NR⁵R⁶; NHO₂NR⁵R⁶; NHO₂R⁸; oder Pyridyl oder Imidazolyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist; bedeutet; R⁵ und R⁶ jeweils unabhängig H, Methyl oder Ethyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, Morpholino-, 4-(NR⁹)-1-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R⁷ H oder tert. Butyl bedeutet; R⁸ Methyl oder CH₂CH₂CH₂NR⁵R⁶ darstellt; und R⁹ H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl bedeutet.

40 7. Verfahren nach Anspruch 6, wobei R¹ Methyl bedeutet; R² n-Propyl darstellt; R³ Ethyl oder n-Propyl ist; R⁴ CH₂NR⁵R⁶, CH₂OCH₂CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CO₂H, CONR⁵R⁶, Br, NHO₂NR⁵R⁶, NHO₂CH₂CH₂CH₂NR⁵R⁶, 2-Pyridyl, 1-Imidazolyl oder 1-Methyl-2-imidazolyl bedeutet; R⁵ und R⁶ zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, 4-Hydroxypiperidino-, Morpholino-, 4-(NR⁹)-1-Piperazinyl- oder 2-Methyl-1-imidazolyl-Gruppe bilden; R⁷ H oder tert. Butyl bedeutet; und R⁹ H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt.

45 8. Verfahren nach Anspruch 7, wobei die hergestellte Verbindung der Formel (I) ausgewählt wird aus:

50 5-[2-Ethoxy-5-(1-methyl-2-imidazolyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;

55 5-[2-Ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;

5-[5 -(4-Acetyl-1-piperazinyl)-acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;

5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on; und

5-(5-Morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;

und pharmazeutisch annehmbaren Salzen hievon.

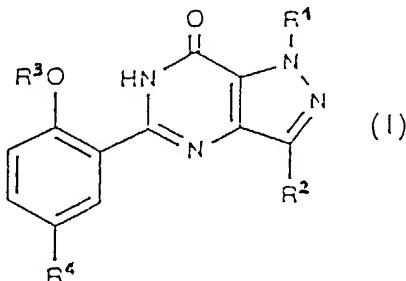
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

5

1. Composé de formule :

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ou sel pharmaceutiquement acceptable d'un tel composé, dans lequel :

R¹ représente H ; alkyle en C₁-C₃ facultativement substitué par un ou plusieurs substituants fluoro ; ou cycloalkyle en C₃-C₅ ;R² représente H, ou alkyle en C₁-C₆ facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C₃-C₆ ;R³ représente alkyle en C₁-C₆ facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C₃-C₆ ; cycloalkyle en C₃-C₅ ; alkényle en C₃-C₆ ; ou alkyne en C₃-C₆ ;R⁴ représente alkyle en C₁-C₄ facultativement substitué par OH, NR⁵R⁶, CN, CONR⁵R⁶ ou CO₂R⁷ ; alkényle en C₂-C₄ facultativement substitué par CN, CONR⁵R⁶ ou CO₂R⁷ ; alcanoyle en C₂-C₄ facultativement substitué par NR⁵R⁶ ; hydroxy(alkyle en C₂-C₄) facultativement substitué par NR⁵R⁶ ; (alcoxy en C₂-C₃)alkyle en C₁-C₂ facultativement substitué par OH ou NR⁵R⁶ ; CONR⁵R⁶ ; CO₂R⁷ ; halogéno ; NR⁵R⁶ ; NHSO₂NR⁵R⁶ ; NHSO₂R⁸ ; phényle ou hétérocyclique dont l'un ou l'autre est facultativement substitué par méthyle ;R⁵ et R⁶ représentent chacun indépendamment H ou alkyle en C₁-C₄ ou, pris ensemble avec l'atome d'azote auquel ils sont liés, forment un groupe pyrrolidinylo, pipéridino, morpholino, 4-(NR⁹)-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou hydroxy ;R⁷ représente H ou alkyle en C₁-C₄ ;R⁸ représente alkyle en C₁-C₃ facultativement substitué par NR⁵R⁶ ;R⁹ représente H ; alkyle en C₁-C₃ facultativement substitué par phényle ; hydroxyalkyle en C₂-C₃ ; ou alcanoyle en C₁-C₄ ; et

hétérocyclique signifie thiényle, pyridyle, pyrazolyle, imidazolyle, triazolyle, oxazolyle, thiazolyle ou pyrimidinyle.

45

2. Composé selon la revendication 1 dans lequel R¹ représente H, méthyle ou éthyle R² représente alkyle en C₁-C₃ ; R³ représente alkyle en C₂-C₃ ; R⁴ représente alkyle en C₁-C₂ facultativement substitué par OH, NR⁵R⁶, CONR⁵R⁶ ou CO₂R⁷ ; acétyle facultativement substitué par NR⁵R⁶ ; hydroxyéthyle substitué par NR⁵R⁶ ; éthoxy-méthyle facultativement substitué par OH ou NR⁵R⁶ ; CH=CHCN ; CH=CHCONR⁵R⁶ ; CH=CHCO₂R⁷ ; CO₂H ; CONR⁵R⁶ ; Br ; NR⁵R⁶ ; NHSO₂NR⁵R⁶ ; NHSO₂R⁸ ; ou pyridyle ou imidazolyle dont l'un ou l'autre est facultativement substitué par méthyle ; R⁵ et R⁶ sont chacun indépendamment choisis entre H, méthyle ou éthyle, ou pris ensemble avec l'atome d'azote auquel ils sont liés forment un groupe pipéridino, morpholino, 4-(NR⁹)-1-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou hydroxy ; R⁷ représente H ou t-butyle ; R⁸ représente méthyle ou CH₂CH₂CH₂NR⁵R⁶ ; et R⁹ représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

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3. Composé selon la revendication 2 dans lequel R¹ représente méthyle ; R² représente n-propyle ; R³ représente éthyle ou n-propyle ; R⁴ représente CH₂NR⁵R⁶, CH₂OCH₂CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CO₂H, CONR⁵R⁶, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂CH₂NR⁵R⁶, 2-pyridyle, 1-imidazolyle ou 1-méthyl-2-imidazolyle ; R⁵ et R⁶ pris ensemble avec l'at-

me d'azote auquel ils sont liés forment un groupe pipéridino, 4-hydroxypipéridino, morpholino, 4- (NR⁹) -1-pipérazinyle ou 2-méthyl-1-imidazolyle ; R⁷ représente H ou t-butyle ; et R⁹ représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

5 4. Composé selon la revendication 3, qui est choisi parmi :

10 la 5-[2-éthoxy-5-(1-méthyl-2-imidazolyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylcarbonyl)-phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[5-(4-acétyl-1-pipérazinyl)acétyl-2-éthoxyphényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ; et
la 5-(5-morpholinoacétyl-2-n-propoxyphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, et leurs sels pharmaceutiquement acceptables.

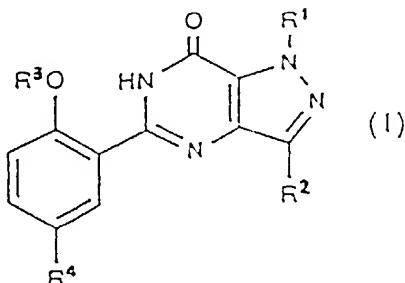
15 5. Composition pharmaceutique comprenant un composé de formule (I), ou un sel pharmaceutiquement acceptable d'un tel composé, selon l'une quelconque des revendications 1 à 4, avec un diluant ou un véhicule pharmaceutiquement acceptable.

20 6. Composé de formule (I), ou sel pharmaceutiquement acceptable d'un tel composé, ou composition pharmaceutique contenant ledit composé ou ledit sel, selon l'une quelconque des revendications 1 à 5, pour une utilisation en médecine.

25 7. Utilisation d'un composé de formule (I), ou d'un sel pharmaceutiquement acceptable d'un tel composé, ou composition pharmaceutique contenant ledit composé ou ledit sel, selon l'une quelconque des revendications 1 à 5, pour la fabrication d'un médicament en vue du traitement de l'angor stable, instable ou variant (Prinzmetal), de l'hypertension, de l'hypertension pulmonaire, de la défaillance cardiaque congestive, de l'athérosclérose, des attaques, de la maladie vasculaire périphérique, des états de libre passage entravé des vaisseaux sanguins, d'asthme chronique, de bronchite, d'asthme allergique, de rhinite allergique, de glaucome ou de maladies caractérisées par des désordres de la motilité intestinale.

35 **Revendications pour les Etats contractants suivants : ES, GR**

1. Procédé de préparation d'un composé de formule :



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ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans lequel:

55 R¹ représente H ; alkyle en C₁-C₃ facultativement substitué par un ou plusieurs substituants fluoro ; ou cycloalkyle en C₃-C₅ ;

R² représente H, ou alkyle en C₁-C₆ facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C₃-C₆ ;

R³ représente alkyle en C₁-C₆ facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C₃-C₆ ; cycloalkyle en C₃-C₅ ; alkényle en C₃-C₆ ; ou alkynyle en C₃-C₆ ;

5 R^4 représente alkyle en C_1 - C_4 facultativement substitué par OH, NR^5R^6 , CN, $CONR^5R^6$ ou CO_2R^7 ; alkényle en C_2 - C_4 facultativement substitué par CN, $CONR^5R^6$ ou CO_2R^7 ; alcanoyle en C_2 - C_4 facultativement substitué par NR^5R^6 ; hydroxy(alkyle en C_2 - C_4) facultativement substitué par NR^5R^6 ; (alcoxy en C_2 - C_3)alkyle en C_1 - C_2 facultativement substitué par OH ou NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halogéno ; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; phényle ou hétérocyclyle dont l'un ou l'autre est facultativement substitué par méthyle ;

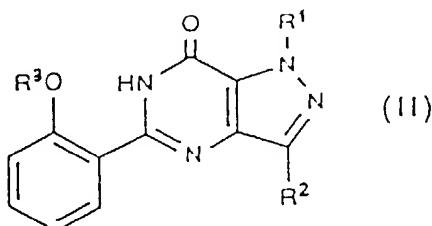
10 R^5 et R^6 représentent chacun indépendamment H ou alkyle en C_1 - C_4 ou, pris ensemble avec l'atome d'azote auquel ils sont liés, forment un groupe pyrrolidinylo, pipéridino, morpholino, 4-(NR^9)-pipérazinyle ou imidazolyle, l'édit groupe étant facultativement substitué par méthyle ou hydroxy ;

15 R^7 représente H ou alkyle en C_1 - C_4 ;

20 R^8 représente alkyle en C_1 - C_3 facultativement substitué par NR^5R^6 ;

25 R^9 représente H ; alkyle en C_1 - C_3 facultativement substitué par phényle ; hydroxyalkyle en C_2 - C_3 ; ou alcanoyle en C_1 - C_4 ; et hétérocyclyle signifie thiényle, pyridyle, pyrazolyle, imidazolyle, triazolyle, oxazolyle, thiazolyle ou pyrimidinyle ;

15 qui consiste à faire réagir un composé de formule (II)



30 dans laquelle R^1 , R^2 et R^3 sont tels que précédemment définis dans cette revendication, pour un composé de formule (I), lorsque R^4 représente :

35 (A) alcanoyle en C_2 - C_4 ou hydroxyalkyle en C_2 - C_4 , avec un halogénure d'acyle de formule (alkyle en C_1 - C_3) COY dans laquelle Y représente halogéno, en présence d'un acide de Lewis, facultativement suivie par la réduction de la cétone résultante en alcool correspondant.

40 (B) alcanoyle en C_2 - C_4 ou hydroxyalkyle en C_2 - C_4 , dont chacun est substitué par NR^5R^6 où R^5 et R^6 sont tels que précédemment définis dans cette revendication, avec un halogénure d'halogénoacyle de formule $X(alkylène en C_1-C_3)COY$ dans laquelle X représente halogéno et Y est tel que précédemment défini dans cette revendication, en présence d'un acide de Lewis, suivie par la réaction de l'halogénocétone résultante, soit avec une amine de formule R^5R^6NH , facultativement suivie par la réduction de l'aminocétone résultante, soit avec une amine protégée de formule R^5NHP , R^6NHP ou $P'NH$ où P et P' sont des groupes amino-protecteurs convenables, facultativement suivie par la réduction de l'aminocétone résultante avant ou après l'élimination de P ou de P' ;

45 (C) alkyle en C_1 - C_4 facultativement substitué par OH, NR^5R^6 , $CONR^5R^6$ ou CO_2R^7 où R^5 , R^6 et R^7 sont tels que précédemment définis dans cette revendication, ou bromo,

50 (i) dans des conditions de chlorométhylation, suivie de la soumission de l'intermédiaire chlorométhyle résultant à, respectivement,

55 (a) une réduction, ou
 (b) une réaction avec un hydroxyde de métal alcalin, ou
 (c) une réaction avec une amine de formule R^5R^6NH , ou
 (d) une réaction avec un cyanure de métal alcalin et facultativement la transformation du nitrile résultant en amide, acide ou ester correspondant ; ou

55 (ii) dans des conditions de bromation aromatique, suivie de la soumission du dérivé bromo résultant à, respectivement:

(a) un échange lithium-brome, suivi de la réaction du dérivé aryl-lithium avec de l'oxyde d'éthylène pour donner le dérivé 2-hydroxyéthyle, ou
 5 (b) la réaction avec de l'alcool allylique, suivie de l'hydrogénéation catalytique de l'alkène pour donner le dérivé 3-hydroxypropyle, ou
 (c) la réaction avec le 3-butèn-1-ol, suivie de l'hydrogénéation catalytique de l'alkène pour donner le dérivé 4-hydroxybutyle,

10 et la transformation facultative de l'un quelconque des alcools précités en alcane amine ou nitrile correspondants par activation de leurs groupes hydroxy respectifs pour donner le chlorure ou le mésylate suivie, respectivement, par la réduction, ou la réaction avec une amine de formule R^5R^6NH , ou la réaction avec un cyanure de métal alcalin et la transformation facultative supplémentaire dudit nitrile en amide ou ester correspondants.

15 (D) alkényle en C_2 - C_4 substitué en 2 par CN, $CONR^5R^6$ ou CO_2R^7 , ou alkyle en C_2 - C_4 substitué en 2 par CN, $CONR^5R^6$, CO_2R^7 ou CH_2NH_2 , où R^5 , R^6 et R^7 sont tels que précédemment définis dans cette revendication, *via* le dérivé bromo du (C) (ii) ci-dessus, avec, respectivement, le nitrile, l'amide ou l'ester α,β -insaturé approprié, suivie facultativement par l'hydrolyse de tout ester résultant, la réduction du groupe alkényle résultant et, dans le cas du nitrile, la réduction ultérieure ou concomitante du groupe nitrile en amine primaire correspondante.

20 (E) alkényle en C_2 - C_4 ou alkyle en C_2 - C_4 , dont chacun est facultativement substitué par CN, $CONR^5R^6$ ou CO_2R^7 , où R^5 , R^6 et R^7 sont tels que précédemment définis dans cette revendication

25 *via* le dérivé bromo de (C) (ii) ci-dessus, avec un réactif d'échange lithium-brome, suivie de la soumission du dérivé aryl-lithium à une formylation, et à la réaction de l'aldéhyde résultant avec le phosphonate ou le sel d'alkyl (en C_1 - C_3)phosphonium approprié éventuellement substitué par CN-, $CONR^5R^6-$, ou CO_2R^7- , facultativement suivie de l'hydrolyse de tout ester résultant et de la réduction du groupe alkényle résultant ;

30 (F) (alcoxy en C_1 - C_3)alkyle en C_1 - C_2 , facultativement substitué par OH ou NR^5R^6 où R^5 et R^6 sont tels que précédemment définis dans cette revendication,

(i) *via* le dérivé chlorométhyle de (C)(i) ci-dessus, avec soit

35 (a) un alcanol en C_2 ou C_3 , soit

(b) un diol en C_2 - C_3 , facultativement suivie par l'activation du groupe hydroxy pour donner le mésylate et la réaction soit avec une amine de formule R^5R^6NH , soit avec une amine protégée de formule R^5NHP , R^6NHP ou P'_2NH où P et P' sont tels que précédemment définis dans cette revendication ; ou

40 (ii) *via* le dérivé bromo de (C)(ii) ci-dessus, avec un réactif d'échange lithium-brome, suivie de la réaction du dérivé aryl-lithium avec de l'oxyde d'éthylène pour donner le dérivé 2-hydroxyéthyle, et l'activation du groupe hydroxy et la réaction ultérieure comme sous (i) (a) ou (i) (b) ;

45 (G) $CONR^5R^6$ ou CO_2R^7 où R^5 , R^6 et R^7 sont tels que précédemment définis dans cette revendication, *via* le dérivé bromo de (C) (ii) ci-dessus, avec un réactif d'échange lithium-brome, suivie par la réaction du dérivé aryl-lithium avec du dioxyde de carbone et la transformation d'une forme convenablement activée de l'acide carboxylique résultant en dérivé amide ou ester par réaction, respectivement, avec une amine de formule R^5R^6NH ou un alcool de formule R^7OH ;

50 (H) NH_2 , halogéno, $NHSO_2NR^5R^6$ ou $NHSO_2R^8$, où halogéno représente fluoro, chloro, bromo, iodo, et R^5 , R^6 et R^8 sont tels que précédemment définis dans cette revendication, dans des conditions de nitration aromatique, suivie de la réduction du composé nitro résultant en amine primaire correspondante et la soumission de ladite amine respectivement à :

(a) une séquence de réaction classique diazotation-halogénéation, ou

(b) la réaction avec soit un halogénure de sulfamoyle de formule $R^5R^6NSO_2$ halogéno, ou un halogénure de sulfonyle de formule R^8SO_2 halogéno, où halogéno est de préférence chloro, soit un sulfamide lorsque R^5 et R^6 représentent tous deux H ;

55 (I) phényle ou hétérocyclique, dont l'un ou l'autre est facultativement substitué par méthyle, *via* le dérivé bromo de (C) (ii) ci-dessus avec

(i) lorsque R^4 est facultativement substitué par phényle ou hétérocyclique lié *via* un atome de carbone, le

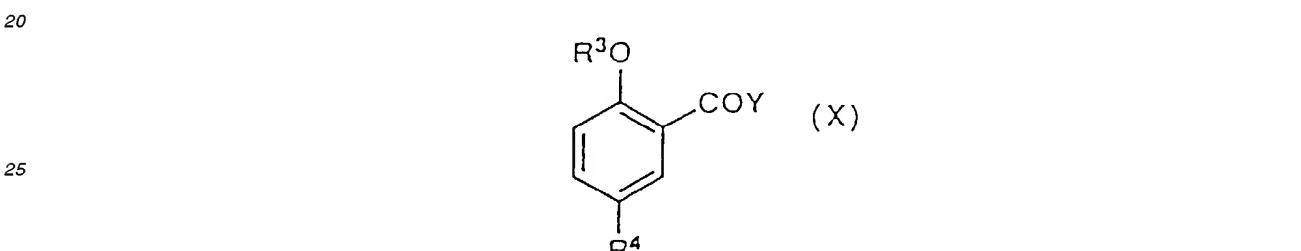
dérivé zincate phényle ou hétérocyclique approprié et facultativement substitué en présence d'un catalyseur de palladium, ou :

(ii) lorsque R⁴ est un hétérocycle lié *via* un atome d'azote, l'hétérocycle approprié en présence de cuivre-bronze, d'iode et d'une base ;

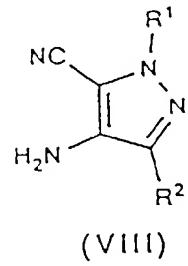
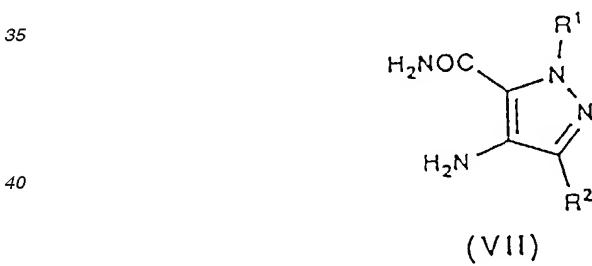
5 suivie dans chaque cas par l'isolation facultative d'un sel pharmaceutiquement acceptable du produit ou la formation d'un tel sel.

10 2. Procédé de préparation d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans laquelle R¹, R², R³ et R⁴ sont tels que précédemment définis dans la revendication 1, qui consiste à faire réagir un composé de formule (II), dans laquelle R³ représente H, et R¹ et R² sont tels que précédemment définis dans la revendication 1, selon l'un quelconque des procédés définis dans la revendication 1, suivi d'une O-alkylation du groupe phénolique pour introduire R³ et facultativement de l'isolation sous la forme d'un sel pharmaceutiquement acceptable du produit ou de la formation d'un tel sel.

15 3. Procédé de préparation d'un composé de formule (I), ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans lequel R¹, R², R³ et R⁴ sont tels que précédemment définis dans la revendication 1, qui consiste à faire réagir un composé de formule (X) :



30 dans laquelle Y représente chloro ou bromo, et R³ et R⁴ sont tels que précédemment définis dans la revendication 1, avec un aminopyrazole soit de formule (VII) soit de formule (VIII)



45 dans lesquelles R¹ et R² sont tels que précédemment définis dans la revendication 1, suivi par la cyclisation des amides résultants respectifs par traitement à l'aide d'une base, facultativement en présence de peroxyde d'hydrogène, et facultativement par l'isolation sous la forme d'un sel pharmaceutiquement acceptable du produit ou par la formation d'un tel sel.

50 4. Procédé selon la revendication 1, dans lequel :

dans (A), Y représente chloro ou bromo, l'acide de Lewis est le chlorure d'aluminium ou le bromure d'aluminium, et l'agent réducteur est le borohydrure de sodium ;

55 dans (B), X et Y représentent chloro ou bromo, P représente benzyle et est enlevé par hydrogénéation catalytique, et P' représente t-butoxycarbonyle et est enlevé en utilisant du chlorure d'hydrogène ;

dans (C) ;

(i) la chlorométhylation est mise en oeuvre en utilisant du paraformaldéhyde et de l'acide chlorhydrique

concentré, et

5 (a) la réduction est effectuée par hydrogénéation catalysée au palladium,
 (b) l'hydroxyde de métal alcalin est l'hydroxyde de sodium ou l'hydroxyde de potassium,
 (c) la réaction avec R^5R^6NH est mise en oeuvre en utilisant un excès de ladite amine,
 (d) le cyanure de métal alcalin est le cyanure de sodium ou le cyanure de potassium ;

10 (ii) la bromation aromatique est mise en oeuvre en utilisant du n-bromosuccinimide et,

15 (a) l'échange lithium-brome est effectué en utilisant du n-butyl-lithium,
 (b) la réaction avec l'alcool allylique est effectué dans des conditions de réaction de Heck,
 (c) la réaction avec le 3-butèn-1-ol est effectuée dans des conditions de réaction de Heck ;

20 dans (D), la réaction avec, respectivement, le nitrile, l'amide ou l'ester α,β -insaturé approprié est effectuée dans des conditions de réaction de Heck en utilisant la tri-*o*-tolylphosphine, l'acétate de palladium(II) et la triéthylamine, l'hydrolyse facultative de l'ester est effectuée en utilisant une solution aqueuse d'hydroxyde de sodium dans le méthanol, la réduction facultative du groupe alkényle est effectuée par hydrogénéation catalysée au palladium, et la réduction facultative ultérieure ou concomitante du groupe nitrile est mise en oeuvre en utilisant du nickel de Raney dans de l'acide acétique glacial ;

25 dans (E), l'échange lithium-brome est effectué en utilisant du n-butyl-lithium, le réactif de formylation est le diméthylformamide et la réduction de l'alkène est effectuée par hydrogénéation catalytique ;

dans (F), la réaction avec

30 (a) un alcool en C_2 ou C_3 est mise en oeuvre en présence d'un équivalent de sodium-métal, ou
 (b) un diol en C_2 ou C_3 est mise en oeuvre en présence d'un équivalent de sodium-métal, le groupe hydroxy est transformé en son mésylate en utilisant du chlorure de mésyle dans de la pyridine comme solvant, et la réaction avec R^5R^6NH est mise en oeuvre en utilisant un excès de ladite amine, et

35 (ii) l'échange lithium-brome est effectué en utilisant du n-butyl-lithium :

40 dans (G), l'échange lithium-brome est effectué en utilisant du n-butyl-lithium et l'acide carboxylique est activé en utilisant un carbodiimide en combinaison avec du 1-hydroxybenzotriazole ;

45 dans (H), la nitration est effectuée en utilisant de l'acide nitrique concentré en combinaison avec de l'acide sulfurique concentré, le composé nitro est réduit par hydrogénéation catalytique, la réaction avec un chlorure de sulfamoyle ou avec un chlorure de sulfonyle est mise en oeuvre en présence d'un excès de pyridine ou de triéthylamine, facultativement en présence de 4-diméthylaminopyridine, et la réaction avec le sulfamide est effectuée à environ 100°C ;

50 dans (I),

40 (i) le catalyseur de palladium est le tétrakis(triphénylphosphine)palladium(0) et le dérivé zincate de phényle ou d'hétérocyclyle facultativement substitué est obtenu à partir du dérivé phényle ou hétérocyclyl-lithium correspondant facultativement substitué et de chlorure de zinc anhydre, et
 (ii) le composé hétérocyclique est présent en excès et la base est le carbonate de potassium anhydre.

55 5. Procédé selon la revendication 2, dans lequel la O-alkylation est effectuée en utilisant le chlorure, bromure ou sulfonate d'alkyle approprié en présence de carbonate de potassium.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel R¹ représente H, méthyle ou éthyle ; R² représente alkyle en C₁-C₃ ; R³ représente alkyle en C₂-C₃ ; R⁴ représente alkyle en C₁-C₂ facultativement substitué par OH, NR⁵R⁶, CONR⁵R⁶ ou CO₂R⁷ ; acétyle facultativement substitué par NR⁵R⁶ ; hydroxyéthyle substitué par NR⁵R⁶ ; éthoxyméthyle facultativement substitué par OH ou NR⁵R⁶ ; CH=CHCN ; CH=CHCONR⁵R⁶ ; CH=CHCO₂R⁷ ; CO₂H ; CONR⁵R⁶ ; Br ; NR⁵R⁶ ; NSO₂NR⁵R⁶ ; NSO₂R⁸ ; ou pyridyle ou imidazolyle dont l'un ou l'autre est facultativement substitué par méthyle ; R⁵ et R⁶ sont chacun indépendamment choisis entre H, méthyle ou éthyle, ou pris ensemble avec l'atome d'azote auquel ils sont liés forment un groupe pipéridino, morpholino, 4-(NR⁹)-1-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou hydroxy ; R⁷ représente H ou t-butyle ; R⁸ représente méthyle ou CH₂CH₂CH₂NR⁵R⁶ ; et R⁹ représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

7. Procédé selon la revendication 6, dans lequel R¹ représente méthyle ; R² représente n-propyle ; R³ représente éthyle ou n-propyle ; R⁴ représente CH₂NR⁵R⁶, CH₂OCH₂CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CO₂H, CONR⁵R⁶, Br, NSO₂NR⁵R⁶, NSO₂CH₂CH₂CH₂NR⁵R⁶, 2-pyridyle, 1-imidazolyle ou 1-méthyl-2-imidazolyle ; R⁵ et R⁶ pris ensemble avec l'atome d'azote auquel ils sont liés forment un groupe pipéridino, 4-hydroxypipéridino, morpholino, 4-(NR⁹)-1-pipérazinyle ou 2-méthyl-1-imidazolyle ; R⁷ représente H ou t-butyle ; et R⁹ représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

8. Procédé selon la revendication 7, dans lequel le composé de formule (I) produit est choisi parmi :

10 la 5-[2-éthoxy-5-(1-méthyl-2-imidazolyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylcarbonyl)-phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 15 la 5-[5-(4-acétyl-1-pipérazinyl)acétyl-2-éthoxy-phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one ;
 la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one ; et
 20 la 5-(5-morpholinoacétyl-2-n-propoxyphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one, et leurs sels pharmaceutiquement acceptables.

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